A large-scale simulation model of pandemic influenza outbreaks for development of dynamic mitigation strategies

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Limited stockpiles of vaccine and antiviral drugs and other resources pose a formidable healthcare delivery challenge for an impending human-to-human transmittable influenza pandemic. The existing preparedness plans by the Center for Disease Control and Health and Human Services strongly underscore the need for efficient mitigation strategies. Such a strategy entails decisions for early response, vaccination, prophylaxis, hospitalization and quarantine enforcement. This paper presents a large-scale simulation model that mimics stochastic propagation of an influenza pandemic controlled by mitigation strategies. The impact of a pandemic is assessed via measures including total numbers of infected, dead, denied hospital admission and denied vaccine/antiviral drugs, and also through an aggregate cost measure incorporating healthcare cost and lost wages. The model considers numerous demographic and community features, daily human activities, vaccination, prophylaxis, hospitalization, social distancing, and hourly accounting of infection spread. The simulation model can serve as the foundation for developing dynamic mitigation strategies. The simulation model is tested on a hypothetical community with over 1 100 000 people. A designed experiment is conducted to examine the statistical significance of a number of model parameters. The experimental outcomes can be used in developing guidelines for strategic use of limited resources by healthcare decision makers. Finally, a Markov decision process model and its simulation-based reinforcement learning framework for developing mitigation strategies are presented. The simulation-based framework is quite comprehensive and general, and can be particularized to other types of infectious disease outbreaks.

Keywords: Pandemic influenza, epidemeology, dynamic mitigation strategy, simulation, resource allocation strategy

1. Introduction

In the event of an avian influenza pandemic outbreak, about 90 000 000 people in the US are expected to be ill and in need of assistance. Most existing contingency plans by the Center for Disease Control and Health and Human Services strongly emphasize the need for efficient and implementable strategies for mitigating pandemic outbreaks (US CDC, 2006; US HHS, 2006). A mitigation strategy incorporates vaccination, prophylaxis, hospitalization and social distancing decisions. Obtaining such a strategy scalable for large communities is a task of staggering complexity requiring a high level of modeling and computing support. Such a need was recently recognized at the joint meeting of the National Academy of Engineering (NAE) and the Institute of Medicine (IOM). The report resulting from the meeting clearly stated the need to "develop both a framework and

an action plan for a systems approach to health care delivery based on a partnership between engineers and health care professionals" (NAE, 2005).

The first major influenza pandemic in recorded history attributed to virus serotype H1N1 took place in 1918–1919. It is estimated that between 40 000 000 and 100 000 000 deaths occurred worldwide. As much as 50% of the US population was infected. In 1957, a H2N2 virus (named Asian Flu) originated in China, quickly spread throughout the world and caused 70 000 deaths in the US. In 1968, an H3N2 virus emerged in Hong Kong for which the fatalities in the US were 34 000 (NIGMS, 2004).

In recent years, a type of bird flu called avian influenza A (H5N1) has emerged. This virus type occurs naturally among wild birds worldwide and can easily spread to domesticated birds (US CDC, 2006; NIGMS, 2004). Since 1977, several cases of transmission of this virus from domesticated birds to humans have been reported. However, the main fear presently in the scientific community is that the constantly mutating variants of influenza A

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virus might adapt over time to infect and spread from humans to humans. Currently, there are 25 known variants of H5N1 viruses and many different combinations of them are possible. The uncertainty about the exact variant of the emerging virus presents an impediment to the design of a potent vaccine, lack of which in sufficient quantity poses a significant challenge to the responsible healthcare authorities.

In the event of a pandemic outbreak, even after the virus subtype is identified, production of a potent vaccine in sufficient quantity could take up to 6 months (Aunins *et al.*, 2000; Fedson and Hant, 2003), too long for the vaccine to be an effective resource in the critical early stage of an outbreak. Even if the emerging virus belongs to a known subtype, the current stockpile of vaccines would be insufficient. Hospital beds, healthcare personnel, antiviral drugs, social distancing and transportation logistic can also be constrained. This makes development of suitable pandemic mitigation strategies a very challenging task, which must consider numerous epidemiological, sociological, logistical and operational factors. Since the devastation from a pandemic could occur very rapidly (perhaps, in a few weeks), it is essential that *scalable* mitigation strategies supported by comprehensive and scientifically valid models are developed beforehand and made available to the healthcare delivery decision makers. Such pre-developed strategies could also serve as valuable tools for healthcare personnel training and preparedness exercises.

The existing literature on pandemic preparedness uniformly echoes the need for strategic planning (Fedson and Hant, 2003; US HHS, 2007; WHO, 2004; IOM, 2004). Most of the papers and reports on pandemic preparedness are focused on qualitative discussions and mock exercises (human simulations). Few studies are available that use either analytical or computer simulation models (Longini and Hill, 2003; Longini *et al.* 2004; NIMGS, 2004; Johns Hopkins Bloomberg School of Public Health, 2005; Patel *et al.*, 2005). The recent work by Patel *et al.* (2005) presents an excellent simulation-based framework under which vaccination distribution strategies can be studied. The concept of Epidemic Prevention Potential (EPP) was introduced in Halloran, Longini, Cowart and Nizam (2002) to measure the effectiveness of different intervention strategies. They developed a simulation model on which they test the EPP of vaccination strategies for seasonal epidemics. The extent of vaccination needed to contain pandemic outbreak is studied in Halloran, Longini, Nizam and Yang (2002), Kaplan *et al.* (2002), and Longini and Hill (2003). Different purposes that are served by vaccines and antiviral drugs in pandemic preparedness are discussed in Monto (2005). The study by Fraser *et al.* (2004) identifies the impact of epidemiological properties of virus on outbreak control strategies such as tracing, isolation and quarantining of symptomatic individuals. Gani and Leach (2004) developed a model to study the impact of delays in implementing outbreak con-

trol measures. An excellent treatment of the economic impact of pandemic influenza outbreak in the US can be found in Meltzer *et al.* (1999).

Our literature exploration has revealed that research efforts have concentrated on: (i) large-scale human simulations at the local level; (ii) qualitative discussions; and (iii) mathematical and computer simulation models that examine individual intervention mechanisms while considering only a small subset of the pandemic parameters. The principle shortcomings of the current literature are as follows. Lessons learned from *human simulations* do not extrapolate to communities with different demographics and to pandemics with different epidemiological properties. It seems almost impossible to construct a purely mathematical paradigm to capture all essential characteristics of a pandemic and its available mitigation actions. This has manifested in the limited scope of the few existing mathematical models. Simulation models and recently developed simulation-based stochastic optimization techniques offer significant promise to alleviate the above shortcomings. However, no such attempt has yet been undertaken to address the challenge of pandemic mitigation. Simulation-based approaches have been reported that account for only a limited number of parameters characterizing a pandemic and associated mitigation actions. The simulation model presented here seeks to overcome some of the above fundamental barriers impeding the development and deployment of computationally tractable decision support models that can consolidate all the major intervention tools (vaccination, prophylaxis, social distancing and hospitalization) under an overall economic impact measure.

This paper presents a simulation model that mimics stochastic propagation of pandemic influenza outbreaks impacted by the decisions made by the healthcare officials in communities with millions of people. The model considers the following.

1. Community features:
   (a) large communities with several population centers and millions of households;
   (b) varying sizes of households based on census data;
   (c) variety of establishments including businesses, factories, schools, churches, public facilities, shopping centers and dining and entertainment centers;
   (d) contact rate for each type of business (number of people contacted by an infected individual per hour, based on the nature of interactions within the establishment, e.g., working, shopping, dining, etc.).
2. Demographic features:
   (a) population distribution based on age, gender, parenthood and occupation;
   (b) daily human activities for both weekdays and weekends subject to social distancing policies in effect.
3. Physiological features:
   (a) health condition of each individual;

    (b) infection susceptibility;
    (c) immunity status;
    (d) vaccination and prophylaxis status.
4. Behavioral features:
    (a) impact on daily schedule;
    (b) propensity and promptness to seek medical assistance in the presence of influenza symptoms;
    (c) conformance to voluntary quarantine;
    (d) probability of violation of mandatory quarantine.
5. Epidemiological features:
    (a) virulence of the virus;
    (b) infection probability based on age, gender, health condition, vaccination status and nature of virus;
    (c) rate of infection spread;
    (d) rate of mortality;
    (e) average lengths of incubation period and disease period;
    (f) effectiveness of vaccine and antiviral drugs.
6. Mitigation-strategy-related features:
    (a) outbreak detection delay of the early warning systems;
    (b) delay in deployment of field responders;
    (c) consideration of limited stockpiles of vaccines and antiviral drugs;
    (d) risk group determination (based on virus virulence, age and health condition) for vaccination, prophylaxis and hospitalization;
    (e) target length of vaccination and prophylaxis periods, i.e., length of time (say, 48 hours) within which the risk groups are to be administered vaccine/antiviral drug based on the availability of healthcare personnel and facilities;
    (f) thresholds for declaration of voluntary quarantine, closing of schools and public facilities, and distribution of protective supplies;
    (g) mandatory (at home) quarantine period;
    (h) degree of monitoring of mandatory quarantine (based on availability of enforcement personnel);
    (i) average length of hospital stay (depending on virus virulence, available bed capacity).

As evident from the above, our simulation program takes a comprehensive account of the stochastic propagation of a pandemic and also the impact of possible decision choices of responsible healthcare agencies. The simulation effectively tracks the hourly changes in the community status through the following: (i) activity, location and disease stage of each individual; (ii) status of mitigation-related actions and resource availabilities; (iii) the numbers of new and cumulative infections and deaths; (iv) number of hospital admission denials; and (v) number of denials of vaccine/antiviral drugs. The simulation also accounts for the economic impact of the pandemic in terms of loss of wages and healthcare cost to the affected population.

Our simulation program can accommodate features specific to pandemic outbreaks of other infectious diseases such as smallpox, pneumonic plague, etc. The program is also suitable for modeling epidemics such as annual influenza outbreaks. A two-level fractional factorial experiment is conducted to examine sensitivities of seven factors (hospital bed capacity, delay in deployment of field responders, average length of hospitalization, percentage of mandatory quarantine violation, percentage of voluntary quarantine conformance, threshold for declaration of voluntary quarantine and target length of vaccination period) toward three of the critical output measures: total number of infected, total number of deaths and the total cost. Statistically significant factors can be used in developing guidelines for the decision makers.

The program integrates all possible decision elements and assesses their performance via detailed measures such as total numbers of infected, dead, denied hospital admission and denied vaccine/antiviral drugs, and also an aggregate measure via the total cost of healthcare and lost wages. Thus, it offers an excellent foundation for simulation-based stochastic optimization of dynamic mitigation strategies. A framework for such a decision optimization based on a Markov decision process model and its reinforcement-learning-based solution strategy are developed and presented.

The rest of the paper is organized as follows. Section 2 discusses in detail various possible elements of pandemic mitigation strategies. Section 3 presents an outline of our simulation model. A detailed numerical study of a sample community of over 1 100 000 inhabitants is conducted in Section 4. Also presented in Section 4 is a sensitivity analysis using a designed statistical experiment. A simulation-based mitigation strategy optimization framework is presented in Section 5. Concluding remarks are given in Section 6.

2. Pandemic mitigation strategies

Dealing effectively with a pandemic influenza outbreak, which, as history shows, is likely to progress rapidly, will require careful planning and strategizing considering factors such as assessment of resource needs and their prioritization, resource deployment, transportation, logistics of information sharing, monitoring and enforcement, and maintenance of law and order. Without a properly planned strategy, the chaos that might ensue might be disastrous causing large-scale fatalities and substantial economic damage. The decision vector constituting a strategy may include the following:

1. Delay in early detection of an outbreak.
2. Delay in deployment of field responders.
3. Vaccination plan:
    (a) risk group (defined by age and health condition);
    (b) target length of vaccination period.
4. Prophylaxis plan:
    (a) risk group (defined by age and health condition);
    (b) target length of prophylaxis period.

5. Hospitalization plan:
   (a) risk group (defined by age and health condition);
   (b) average hospitalization period.
6. Social distancing plan:
   (a) declaration of voluntary quarantine;
   (b) average length of mandatory quarantine for sick who are denied hospital admission;
   (c) extent of monitoring for mandatory quarantine.

The first two elements of the decision vector concerning delays in early detection and deployment of field responders are static (one-time) decisions, which are made based on availability and effectiveness of early warning systems and the cost of deployment readiness. The rest of the decision elements are dynamic since they are evaluated periodically and their values are chosen based on the state of the pandemic. For example, in the early stage of the pandemic, a decision maker might define a risk group for vaccination primarily based on available stockpile and knowledge from past pandemic outbreaks. However, as the pandemic progresses and the demographics of the infected population become available, the decision maker might redefine the risk group accordingly. The state of the pandemic can be defined as a vector with the following elements: total number of infected, total number of deaths, rate of infection, mortality rate, remaining stockpiles of vaccine and antiviral drugs, available vaccine and antiviral drug administration capacity and the available hospital bed capacity.

3. A large-scale simulation model

The simulation model is designed to mimic the daily activities of the people of a large community affected by an outbreak. The model incorporates a set of decisions, which can be enforced by the healthcare delivery authorities, and the impacts of these decisions on the health-related attributes and daily activities of the people. The model is developed using the C++ programming language and can be implemented on a desktop computer. The model was tested for communities having up to over a million people on a Pentium 4 PC with 1 GB memory. For a population of size approximately 100 000, the program took about 30 seconds for each day of simulation. For a community of 400 000 households with over 1 100 000 people, the program took about 50 minutes for each simulation day. Such a simulation model can exploit national high-performance computing cyberinfrastructure (e.g., TeraGrid) to perform the very-large-scale computations necessary to develop and test strategic and tactical mitigation decisions for large metropolitan communities. It may be noted that such simulation models can also be used offline for synthesizing various *a priori* decision alternatives (through "what-if" analysis), in which case the run-times could be of secondary importance. Before discussing some of the major elements of the simulation model, we present a pseudo-code version of the main program via Fig. 1 to provide an idea of the program structure.

3.1. *Infection spread mechanism*

Figure 2 shows an outline of the mechanism used in the simulation model for detailed hourly accounting of the infection spread. The simulation runs in a loop for a prespecified number of days, hour by hour for each day. At the beginning of each day, every member of the community is assigned his/her daily schedule (on an hourly basis). The schedule is dictated by the day of the week and a variety of personal and pandemic-related factors. At the end of each hour, the model scans every community establishment (offices, factories, schools and public facilities, businesses, stores, etc.). The scan identifies, for each establishment including workplaces, the set of people that are present during that hour including those who are contagious. Each contagious individual generates new contacts (chosen randomly from the non-infected), the number of which is prespecified depending on the type of the establishment, its assumed typical human interaction pattern and the number of contagious individuals present. Each contact either becomes infected or is able to fight the virus off, which depends on his/her age, health condition, vaccination status, virulence of the virus and the state of the pandemic. A disease clock for each infected individual is maintained and hourly advanced to identify various phases of his/her disease.

3.2. *Post-contact scenarios*

Figure 3 depicts various scenarios that an infected individual is likely to go through. Given the large percentage of uninsured population and the difficulties often faced in seeking medical assistance, particularly in the United States, a probability exists that an infected individual will not see a doctor. It is also considered that, before a pandemic declaration is made, people with symptoms might wait for a random amount of time before seeking medical aid. Those who actually seek medical aid are admitted to the hospital depending on their medical condition, hospital admission policy and bed availability. Those not admitted are put under a mandatory home quarantine. Prespecified lengths of time are allocated for hospital stay and home quarantine. Family members of infected/quarantined individuals are not considered to be at higher risk of infection; however, this can be incorporated into existing simulation as a future consideration. It is assumed that a percentage of those home quarantined will violate the restrictions in the early stage of disease and will add to the spread. Since the stockpile of antiviral drugs could be limited, it is also expected that all those quarantined at home might not receive antiviral drugs. The model also considers a certain mortality rate depending on age, health condition, prophylaxis status and the effectiveness of antiviral drugs. Recovered

```
Main program
{
        generate_businesses();// create community business & other establishments
        generate_entities(); // create population centers, households, and people
                                    with all their attributes

        //bring an infected person to the community by advancing the disease clock
           of a randomly chosen individual beyond the incubation period
        community[(int)uni(1,N)].disease_clock = incubation_period+1;

        // simulation begins
        while (t_now < max_days*24) { // stopping criterion
                int d = 1+t_now/24; // a new day begins ...
        // assign schedules to everyone at the beginning of the day depending
            on day of the week, employment and workplace attributes, and quarantine

                if (conditions to call for voluntary quarantine are satisfied)
                   //kids stay home and adult activities outside of home are reduced
                        assign_voluntary_quarantine_schedule();
                else assign_regular_schedule(d);

                // simulate hourly activities from 08:00 am till 07:00 pm
                for (int hr = 8; hr <= 19; ++hr) {
                        contact(hr); // checks for new contacts at all establishments
                        infection(); // checks if a contact should be infected
                        disease_progress(); // for each infected individual update
                                                disease/quarantine/hospitalization status
                        // condition to check if a pandemic is declared
                if (number_visits_to_doctor >= field_responders_in_flag)
                        field_responders_move_time = t_now + field_responders_delay;
                        //delay indicates time lag between pandemic declaration and
                        actual deployment of responders
                        // condition to check if field responders have been deployed
                if (t_now >= field_responders_move_time) {
                        vaccination(); // alters vaccination status of the risk group
                        antiviral();} // alters prophylaxis status of the risk group
                visit_doctor_mandatory_quarantine(); // accounts for doctor visits and
                                                mandatory quarantine either at
                                                hospital or at home
                ++t_now;}
                // simulate hourly from 20:00 pm till 07:00 am
                for (int hr = 20; hr <= 24+7; ++hr) {
                        disease_progress(); ++t_now;}
                stat(); // collects statistics on pandemic state
        }
        cost(); // calculates the total cost of healthcare and lost wages
}
```

Fig. 1. Pseudo-code version of the main program.

individuals are assumed to develop full immunity to subsequent infection.

3.3. *Mitigation decision mechanism*

As shown in Fig. 4, the decision process suffers from two unavoidable initial delays, namely early detection delay and the deployment delay of field responders. The early detec-

tion delay results from the need for a minimum sample size for the statistical methods to produce a warning signal without excessive Type I or Type II errors, for which acceptable levels are decided by the decision makers. Deployment delay is a function of resource availability, and hence the decision makers have the power to control the length of this delay. The above decisions are made only once. The remaining elements of the decision vector, vaccination plan, prophylaxis
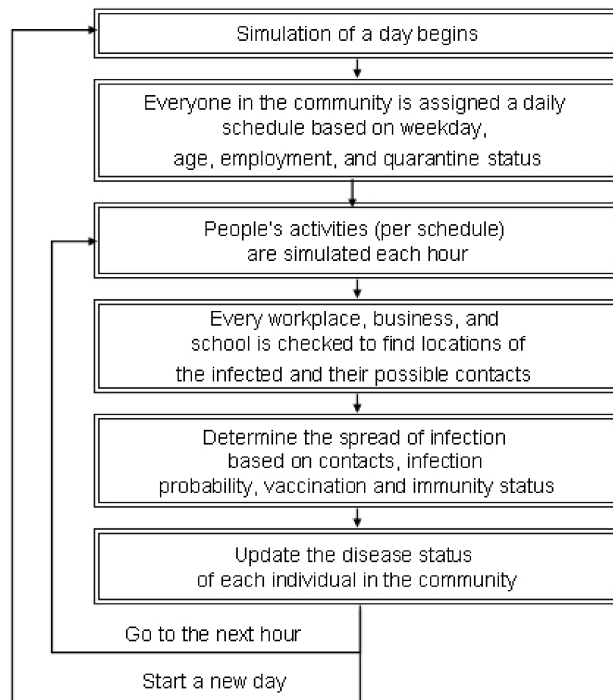
Fig. 2. Tracking of infection spread.

plan, social distancing plan and hospitalization plan, are system state dependent. These are reviewed in light of the system state and are modified as often as necessary. The plans and their constituents are depicted in the figure.

The impacts of the decision are measured in terms of the numbers of infected and dead, and also via total cost of medical care and lost wages.

3.3.1. *Vaccination and prophylaxis*

The simulation model considers fixed stockpiles of vaccine and antiviral drugs. Declaration of a pandemic is triggered by a predetermined number of confirmed cases. Upon declaration, the healthcare authorities choose plans for vaccination and prophylaxis. Both of these plans consist of two decisions: risk group and rate of administration. The risk group, defined by age, identifies those eligible to receive vaccine/antiviral drugs. The rate of administration is a function of the number of people in the risk group and the target period of administration. Selection of risk group is primarily guided by the stockpile, while the rate of administration depends on the availabilities of healthcare personnel and facilities, and also transportation and other logistics. Field responders are assumed to be pre-vaccinated and have full immunity. Hence, the available healthcare capacity is assumed to be unaffected during the course of the pandemic. The model considers the effectiveness of both vaccine and antiviral drugs by reducing the probability of infection and mortality, respectively. Vaccination status is tracked for each individual, which makes it possible to examine the impact of "herd immunity" on an outbreak by assigning a large percentage of the population a "yes" for the vaccination status.
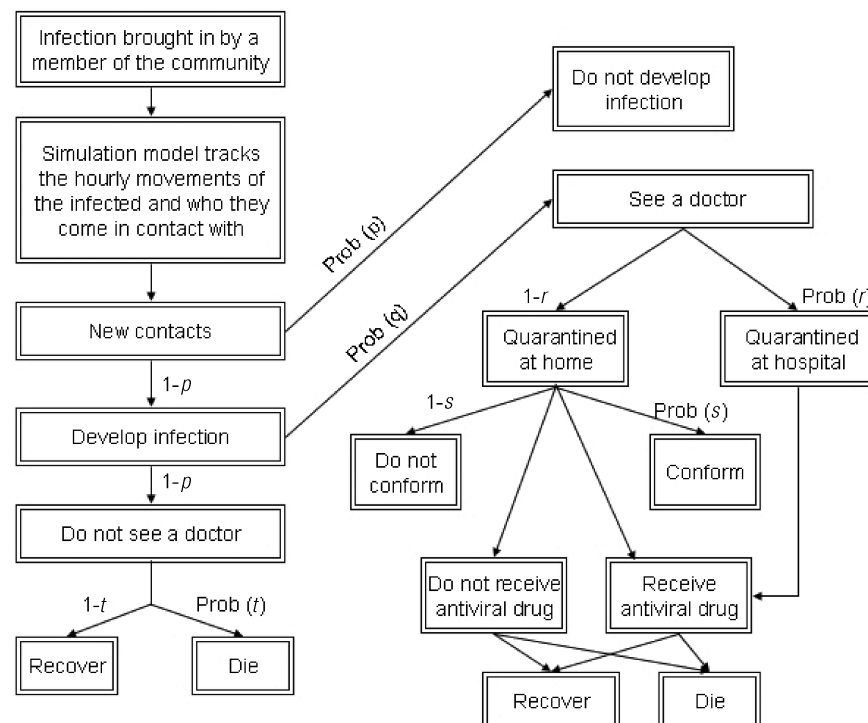

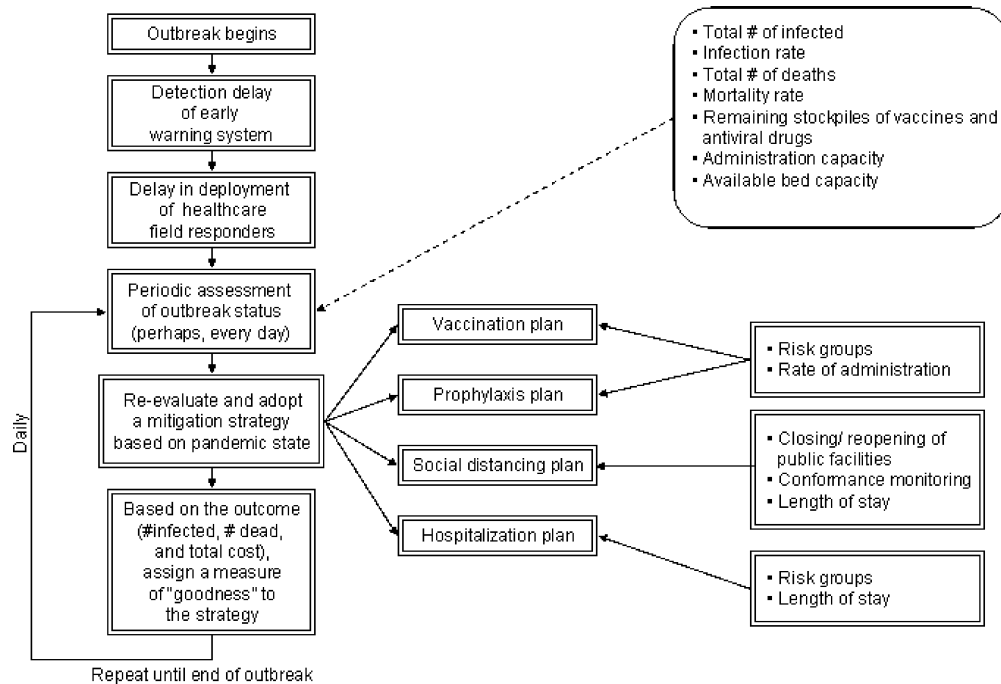**Fig. 3.** Post-contact scenarios for an infected individual.

Fig. 4. Decision process of pandemic mitigation.

3.3.2. *Social distancing and hospitalization*

Two types of social distancing are considered: voluntary quarantine and mandatory quarantine. A voluntary quarantine declaration is based on a prespecified number of confirmed cases and it allows for closing of schools and other public facilities. It is considered that a percentage of the people working in privately owned businesses would not go to work and reduce their outside activities. It is also considered that upon declaration of voluntary quarantine, people will take precautionary measures leading to reduction in infection probability. Mandatory quarantine can be either at home or at hospital. Since the hospital beds will be insufficient, the model considers a hospital admission plan consisting of risk group and average length of hospital stay. Those deemed able to recover at home (not part of the risk group) or are unable to be provided with a hospital bed, are asked to be quarantined at home.

4. A large community as a testbed

To demonstrate that the simulation model could serve as a reliable tool for an accurate assessment of the devastation of an impending pandemic, and also how it could support the challenging task of pandemic mitigation, the model was implemented on a sample problem involving a hypothetical community with over 1 100 000 people. The demonstration is accomplished in the following steps: building the sample community, model validation, pandemic impact assessment and decision support.

4.1. *Sample problem*

All critical considerations for the simulation model are presented in Sections 3.1 through 3.3 and Figs. 2, 3 and 4. The following parameter values were used for the sample problem:

- four population centers;
- 100 000 households in each center;
- nine different household types consisting of different combinations of up to five members (adults and children);
- adults grouped into two age groups and the children grouped into five age groups;
- each adult has three health conditions and the children have two;
- 13 types of community establishments with a total of 52;
- each establishment type has probabilities of being a workplace, place for weekday after work errand, place for weekend errand, and place for errand during voluntary quarantine, human interaction pattern (number of contacts per contagious person);
- available stockpiles of vaccines and antiviral drugs of 250 000 for each;
- six different base rates of infection and mortality based on age and gender (gender is considered in case a specific gender becomes more prone to the virus);
- five degrees of virulence of the virus;
- three phases of disease progress: incubation (not contagious), contagious, and recovery (not contagious);
- early detection delay of 48 hours;
- deployment delay of five confirmed cases;

- threshold for declaration of voluntary quarantine of 500 confirmed cases;
- vaccine and prophylaxis risk groups: below 10 and above 70 years old. Since the model tracks many attributes of each person including age and health condition, it is possible to adopt more general definitions of risk groups (e.g., vaccination of individuals with immune-compromised systems, children less than 6 months and allergic individuals) and administration scheme (e.g., two vaccine doses, prioritization within a risk group);
- target vaccination and prophylaxis period of 40 hours;
- average hospitalization period of 72 hours;
- vaccine and antiviral drug effectiveness of 0.4 and 0.3, respectively (as the model tracks age of all individuals, implementation of age-dependent effectiveness is also possible);
- voluntary quarantine conformance probability of 0.5;
- violation probability of mandatory home quarantine of 0.5; and
- mandatory home quarantine period 120 hours;
- medical cost and lost wage estimates as per Meltzer *et al.* (1999), which are inflation adjusted to 2006 as per Halfhill (2006).

Since lack of sufficient vaccine availability is a major issue, mass vaccination prior to an outbreak to develop *herd immunity* was not considered in the sample problem. Though the community presented in the sample problem is not based on data from an actual community, its features are similar to those of communities that are found in the United States.

4.2. *Model validation*

Validation of our simulation model presents a difficult challenge due to little or no availability of historical pandemic data that can be extrapolated to the present societal context. Difficulty also stems from the scant knowledge about the virus itself, even among healthcare professionals. Hence, we adopted the following steps to ensure sufficient model validity: (i) continuous feedback and cross-validation of the model by medical practitioners, epidemiologists and bio-statisticians; (ii) gathering suggestions and feedback during presentations at local epidemiologic forums; and (iii) rigorous examination of output data for sample problems with various parameter combinations. The above steps resulted in very significant alterations and improvements of the model during its developmental period. Currently, we are planning to implement our model for annual (interpandemic) influenza outbreaks in the Tampa Bay region. This plan is proposed and supported by the local health officials responsible for healthcare delivery in the event of an outbreak. We are currently in the process of gathering data.

4.3. *Pandemic impact assessment*

To demonstrate the ability of our model to provide support for pandemic impact assessment, ten different exploratory scenarios of the testbed problem were simulated. The recorded statistics include number of new infections, cumulative infections, cumulative number of visits to the doctor, remaining stockpiles of vaccines and antiviral drugs, number of denied hospital admission, and cumulative number of dead. We also collected the total cost over a period of time for each scenario. The scenarios were created by varying some of the key input and decision parameters, as shown in Table 1.

Case 1 represents the base case. Variations in the parameter values in cases 2 through 10 were adopted arbitrarily, with the only purpose of demonstrating the potential of the model to support healthcare decision making. If deemed appropriate, additional parameters can be incorporated (e.g., the variance of length of hospital stay in addition to the average length). The last three columns of the table show three of the performance measures. The daily values of these measures were also recorded to examine their trends. Two such trend plots for cases 1 and 10 are shown in Figs. 5 and 6.

Table 1. Results from the testbed problem scenarios

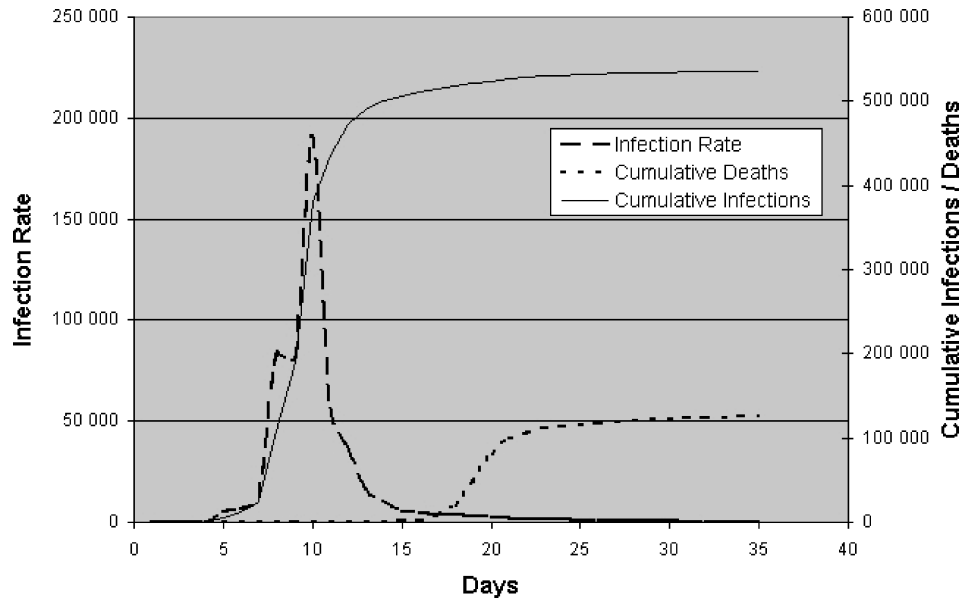| Case	Hospital bed capacity (number of beds)	Delay in deployment of field responders (hours)	Average length of hospital stay (hours)	Percentage of mandatory quarantine violation (%)	Target period of vaccination (hours)	Percentage of voluntary quarantine conformance (%)	Threshold for declaration of voluntary quarantine (number of cases)	Cumulative total of infected	Cumulative number of deaths	Total cost ($ × 10^6)
1	5000	48	72	30	40	50	500	535 531	125 254	129 249.83
2	5000	48	72	50	72	80	2000	523 779	120 263	122 997.52
3	5000	48	96	50	72	50	500	540 210	127 147	130 429.33
4	5000	96	72	50	40	80	500	561 260	136 166	136 723.97
5	5000	96	96	30	72	80	500	570 284	139 875	139 747.19
6	5000	96	96	50	40	50	2000	544 898	128 948	129 868.32
7	7000	48	72	30	40	50	2000	526 345	121 346	124 745.91
8	7000	48	72	50	72	80	500	539 528	126 792	130 077.84
9	7000	48	96	30	40	80	500	534 749	124 682	128 513.07
10	7000	48	96	50	72	50	2000	528 614	122 279	124 944.58

Fig. 5. Trends for infection rate and cumulative values of infected and dead: case 1.

The trend plots clearly show some of the pandemic impacts and their dynamics over time, which can serve as valuable inputs for the decision makers. For example, the plots of the infection rates show distinct differences in their values, slopes and initial patterns. The infections in case 1 happen in a shorter time span compared to case 10, with the maximum rate of case 1 being nearly 75% higher. The plots for the cumulative number of infected are comparable, however, case 1 reaches its maximum value about 2 days earlier. Since deaths can only result from those who are infected, the curve showing cumulative deaths has a very

similar shape to that of cumulative infections. The average delay of the occurrence of death from the day of infection is clearly manifested by the lag between the two curves. Due to the faster rise in infection in case 1, its cumulative deaths curve reaches its maximum value sooner.

4.4. *Decision support*

Though the trend plots discussed in the above section are informative, they lack in providing definitive guidance to the decision makers in isolating the significant factors, which
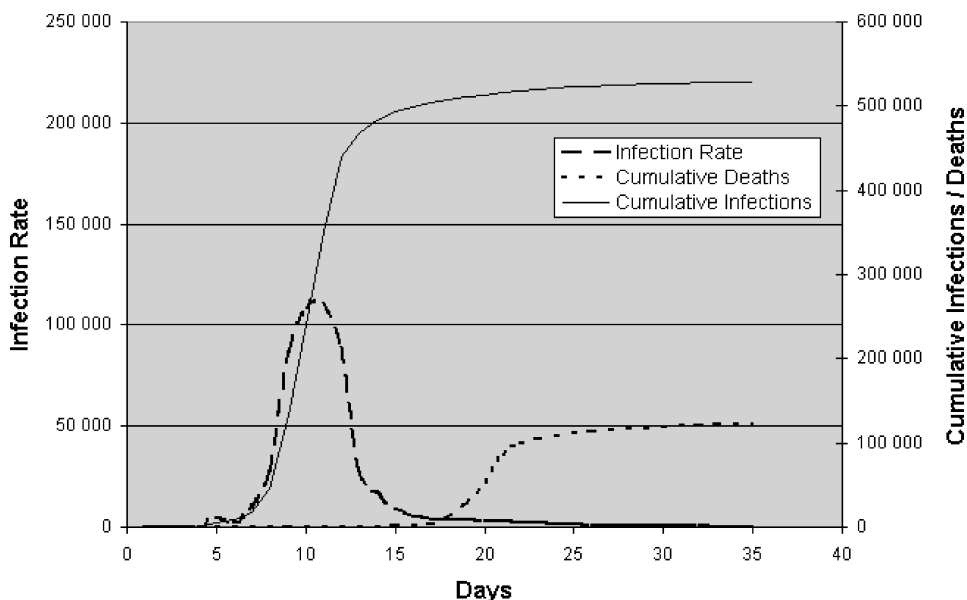

Fig. 6. Trends for infection rate and cumulative values of infected and dead: case 10.

Table 2. Factor values for two-level experimental design

Factor label	Factor name	Low level (1)	High level (2)
A	Hospital bed capacity	5000	7000
B	Delay in deployment of field responders	48	96
C	Average length of hospitalization	72	96
D	Percentage of mandatory quarantine violation	0.3	0.5
E	Target length of vaccination period	40	72
F	Percentage of voluntary quarantine conformance	0.5	0.8
G	Threshold for declaration of voluntary guarantine	500	2000

is required to develop a mitigation strategy. To address the above concern, we conducted a two-level fractional factorial designed statistical experiment. The seven input factors chosen for the experiment are: hospital bed capacity, delay in deployment of field responders, average length of hospitalization, percentage of mandatory quarantine violation, percentage of voluntary quarantine conformance, threshold for declaration of voluntary quarantine and target length of vaccination period. The choice of these factors was done as follows. The rather large number of input and decision factors were classified into two categories: perceived to be significant and potentially significant. The potentially significant factors were chosen for the study. The studied factors and their two different levels (low and high) are shown in Table 2. The analysis was conducted with respect to three different output measures: cumulative number of infections, cumulative number of deaths,

and the total cost of healthcare and lost wages. The choice of a two-level fractional factorial experiment was primarily motivated by our desire to limit the number of experiments. Based on the knowledge of the influence of the above factors on the output measures, any interactions among the factors appeared highly unlikely. Hence, we chose to focus our attention on the main factors only. The fractional factorial design used for the study is a L16 Taguchi array, which allowed for testing significance of seven input factors leaving eight columns (eight degrees of freedom) for error assessment. In the interest of computational time, we used a smaller-sized community (compared to the testbed described earlier) with the following changes in the parameter values: 10 000 households in each population center giving a total of approximately 111 000 people, 25 000 doses each of vaccines and antiviral drugs, hospital bed capacity of 500 and voluntary quarantine threshold of 500 doctor visits. The 16 experimental combinations and the corresponding output measure values are shown in Table 3.

4.4.1. *ANOVA: sensitivity analysis*

The results of the analysis of variance conducted on the data representing cumulative number of infections in Table 4 are presented in Table 4. As shown, for the chosen parameter values of the sample problem, four of the seven factors are found to be statistically significant. These factors are: delay in deployment of field responders (B), percentage of mandatory quarantine violation (D), target length of vaccination period (E) and percentage of voluntary quarantine conformance (F). These were also the only significant factors for the other two performance measures, namely cumulative number of dead and total cost. Since all of the significant factors are decision variables, this information can be used

Table 3. L16 experiment array with output data

Trial	(1) A	(2) B	(3)	(4) C	(5)	(6)	(7)	(8) D	(9)	(10) E	(11)	(12) F	(13)	(14)	(15) G	Cumulative number infected	Cumulative number dead	Total cost ($\$\times 10^6$)
1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	57 402	14 301	14 150
2	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	57 944	14 394	14 303
3	1	1	1	2	2	2	2	1	1	1	1	2	2	2	2	57 320	14 258	14 171
4	1	1	1	2	2	2	2	2	2	2	2	1	1	1	1	58 874	14 769	14 487
5	1	2	2	1	1	2	2	1	1	2	2	1	1	2	2	60 509	15 489	15 147
6	1	2	2	1	1	2	2	2	2	1	1	2	2	1	1	59 995	15 269	14 894
7	1	2	2	2	2	1	1	1	1	2	2	2	2	1	1	59 981	15 271	14 950
8	1	2	2	2	2	1	1	2	2	1	1	1	1	2	2	60 241	15 538	15 010
9	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	57 215	14 064	14 027
10	2	1	2	1	2	1	2	2	1	2	1	2	1	2	1	56 046	14 432	14 234
11	2	1	2	2	1	2	1	1	2	1	2	2	1	2	1	57 300	14 039	13 879
12	2	1	2	2	1	2	1	2	1	2	1	1	2	1	2	58 496	14 611	14 456
13	2	2	1	1	2	2	1	1	2	2	1	1	2	2	1	60 348	15 588	15 176
14	2	2	1	1	2	2	1	2	1	1	2	2	1	1	2	59 884	15 256	14 974
15	2	2	1	2	1	1	2	1	2	2	1	2	1	1	2	60 152	15 398	14 946
16	2	2	1	2	1	1	2	2	1	1	2	1	2	2	1	60 514	15 641	15 231

Table 4. ANOVA results

Factors	Sum of squares	df	F0	P-values	Outcome
A	6045.06	1	0.213	0.656 383 798	not significant
B	22 626 570.56	1	798.929	2.6522×10^{-9}	significant
C	147 264.06	1	5.200	0.052 046 865	not significant
D	886 893.06	1	31.315	0.000 512 619	significant
E	1253 840.06	1	44.272	0.000 160 188	significant
F	553 908.06	1	19.558	0.002 219 238	significant
G	30 537.56	1	1.078	0.329 451 712	not significant
Error	226 570.00	8			

to define an effective decision space for the learning-based mitigation strategy optimization process discussed in the next section.

5. Mitigation strategy optimization framework

In the previous section, we demonstrated through a numerical study that the proposed model can effectively capture the dynamics of pandemic spread constrained by a variety of possible mitigation plans that can be chosen by responsible authorities. As alluded to earlier, a mitigation strategy is a collection of decision vectors (containing the four plans, each of which is a vector by itself) indexed by time. The output of the model measures the "goodness" of a chosen strategy. However, since the strategy space is extremely large, it is imperative to develop an approach that can sweep through the space and identify a good strategy. In this section, we present a framework for simulation-based stochastic optimization, which can be exploited to select a strategy with an objective of minimizing a chosen output measure.

In what follows, we refer to the community affected by an outbreak as the *system*. Define system state at any time t as $X_t = (N_i, N_d, R_i, R_d, S_v, S_p, C_v, C_p, C_h)$, where:

N_i = cumulative number of infected in the system;
N_d = cumulative number of dead in the system;
R_i = daily rate of infection (daily increment in the number of new infected cases);
R_d = daily rate of mortality (the daily increment in the number of new dead cases);
S_v = remaining stockpile of vaccine;
S_p = remaining stockpile of prophylactic (antiviral) drug;
C_v = available vaccine administration capacity;
C_p = available prophylactic drug administration capacity;
C_h = available hospital bed capacity.

Define a random process $\mathbf{X} = \{X_t : t \in \mathbf{R}^+\}$ as the pandemic spread process. We now define a subset of the above process that is embedded at the decision epochs. Let T_n denote the time of the nth decision epoch during the pandemic evolution. Let the system state at time T_n be denoted by X_n.

Define two random processes as

$$\mathcal{T} = \{T_n : n \in \mathbf{N}\} \rightarrow \text{ decision time process,} \quad (1)$$
$$\mathcal{X} = \{X_n : n \in \mathbf{N}\} \rightarrow \text{ decision state process.} \quad (2)$$

Define the decision vector at the nth decision epoch as, $\mathbf{D}_n = (\mathbf{V}, \mathbf{P}, \mathbf{Q}, \mathbf{H})$, where

$\mathbf{V}$ = the vaccination plan vector (r_v, l_v);
$\mathbf{P}$ = the prophylaxis plan vector (r_p, l_p);
$\mathbf{Q}$ = the quarantine plan vector (q^v, q_m^m, q_l^m); and
$\mathbf{H}$ = the hospital admission plan vector (r_h, l_h)

where

- r_v, r_p, r_h represent the risk groups for vaccination, prophylaxis and hospitalization, respectively, which depend on age and health condition;
- l_v, l_p represent the target lengths of vaccination and prophylaxis periods, respectively;
- l_h represents the average length of hospital stay;
- $q^v = (0, 1)$ represents state of voluntary quarantine;
- q_m^m, q_l^m denote the level and the length of monitoring for in-home mandatory quarantine, respectively.

A decision process is defined as

$$\mathcal{D} = \{D_n : n \in \mathbf{N}\}.$$

If we consider that the decisions are reviewed at equal intervals of time during a pandemic evolution, e.g., every day, so that $T_{n+1} - T_n = 1$ day, then the decision state process $\mathcal{X}$ is a Markov chain. The pandemic mitigation process can then be characterized as the joint process $(\mathcal{X}, \mathcal{D})$, which is a Markov Decision Process (MDP).

5.1. *Obtaining a pandemic mitigation strategy*

Optimal methods of solving a MDP are value and policy iterations (Puterman, 1994). If minimizing the total cost is used as criterion for optimization, then the above algorithms are based on solving Bellman's optimality equation given as

$$\mathcal{V}(j) = \min_{a \in A_j} \left\{ r(j, a) + \beta \sum_{k \in E} p(j, a, k) \mathcal{V}(k) \right\}, \quad (3)$$

where

$\mathcal{V}(j)$ = the expected discounted value (cost) of the system starting at state j;
A_j = the set of available decisions at state j;
$r(j, a)$ = the immediate reward (cost) of choosing decision a in state j;
β = the discounting factor;
E = the system state space; and
$p(j, a, k)$ = the one-step transition probability under action a.

For problems with very large state and decision spaces with complex interactions among them, as in the pandemic

mitigation problem, obtaining the transition probabilities is almost impossible. Moreover, the value iteration algorithm requires synchronous updating of values for all the states in every iteration, which is difficult. Policy iteration requires the solution of a system of linear equations, with the number of equations equal to the cardinality of the state space, in each iteration of the algorithm. Therefore, we propose the use of the simulation-based stochastic optimization approach (Reinforcement Learning (RL), in particular), which has recently been applied successfully to solve complex decision making problems (Kaelbling *et al.* 1996; Mahadevan, 1996; Das *et al.*, 1999; Ravulapati *et al.*, 2002; Gosavi, 2004). In this approach, the simulation model obviates the need for transition probabilities, and the values are updated asynchronously (one at a time) reducing the computational burden. For solving discounted reward MDPs, provably convergent and optimal seeking RL algorithms exist in the literature. A sketch of an RL algorithm that can be used to obtain a mitigation strategy is presented below.

5.2. *An RL algorithm*

Initialize the reinforcement values $R(j, a)$ (synonymous to the values $V(j, a)$ in Bellman's equation) for all states $j \in E$, and all decision $a \in A$ to zeros and step count $n = 1$. Select initial value for the learning rate α_n (usually small, e.g., 0.01) and exploration probability γ_n (say, 0.3), parameters needed to decay α_n and γ_n during the learning process, and a stopping criterion *Maxcycles* (maximum number of pandemic cycles of say 90 days each to be simulated, which can be determined through initial trials). The stopping criterion is chosen such that it allows sufficient time for the R-values to converge.

Initialize *cycle* = 1, and start simulation.

Step 1. If the current system state is j, perform the following steps.

Step 2. Choose a decision (say, a) for which the R-value in state j ($R(j, a)$) is minimum (a greedy strategy) with probability $(1 - \gamma_n)$, or an arbitrary decision from the available decision set minus the greedy action with probability γ_n. If the state has not been visited yet and all R-values are zeros, select an arbitrary decision.

Step 3. Simulate the chosen action, proceed to the next decision epoch and determine the new state (say, k).

Step 4. Update the reinforcement value of $R(j, a)$ as follows:

$$R_{\text{new}}(j, a) = (1 - \alpha_n)R_{\text{old}}(j, a) + \beta[r(j, a) + \min_{b \in A_k} R_{\text{old}}(k, b)],$$

where $r(j, a)$ denotes the immediate cost of choosing decision a in state j, and β is the discount factor.

Step 5. $n \leftarrow n + 1$.

Step 6. Decay α_n and γ_n using a suitable method.

Step 7. If $n \leq 90$ (length of a pandemic cycle), repeat the numbered steps above with $j \leftarrow k$,
else, $n \leftarrow 1$, *cycle* $\leftarrow$ *cycle* + 1.
If *cycles* $\leq$ *Maxcycles*, repeat the numbered steps above,
else, rerun the simulation for a number of cycles using the learned R-values and assess the average discounted cost of pandemic.

6. Conclusions

The need for effective mitigation strategies is well recognized and documented in federal and state level pandemic preparedness publications. However, existing scientific methodologies are limited to either human simulations or mathematical and computer simulation models with limited scope. This paper presents a comprehensive large-scale simulation model for supporting development of mitigation strategies. The simulation model incorporates a variety of decision factors related to plans for vaccination, prophylaxis, social distancing and hospital admission. The model offers a variety of performance measures including an aggregate cost measure. A hypothetical community of over 1 100 000 people was used in demonstrating the utility of the simulation model. Scenarios were created by varying some of the key input and decision parameters, for which three performance measures (cumulative numbers of infected and dead, and total cost of medical care and lost wages) are presented. A statistical designed experiment was used to show how factors with significant impact on a performance measure can be identified. The problem of mitigating a pandemic outbreak is modeled as an MDP. A framework for solving the MDP using a simulation-based RL algorithm is presented.

The simulation model, though quite comprehensive, offers many other possible ways of enhancement, e.g., consideration of proportion of transmission occurring prior to symptoms (Fraser *et al.*, 2004), change in the virility of the virus with pandemic progress and availability of more potent vaccines and antiviral drugs during the course of an outbreak. Validation of the simulation model with actual outbreak data is essential for its widespread recognition and application. Such a validation task is very challenging since it requires the coordination with a variety of healthcare agencies (government and private) and access to archived data. The approach for learning-based mitigation strategy optimization, as presented here, is novel, but must overcome many difficulties before its successful implementation. A primary difficulty stems from the need to isolate the impact (e.g., cost) of a decision, since the impacts are not readily realized and might be compounded with other decisions. Without a clear strategy to assess this impact (which is referred to as the *immediate cost*, $r(j, a)$), learning of the reinforcement values will be incoherent. We are currently

working on these issues and plan to document our findings in future publications. An example of such an RL application in the context of finding efficient medical diagnosis strategies can be found in one of our recently published works (Fakih and Das, 2006).

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References

Aunins, J.G., Lee, A.L. and Volkin, D.B. (2000) *Vaccine Production* (second edn.). CRC Press LLC, Boca Raton, FL.

Das, T., Gosavi, A., Mahadevan, S. and Marchalleck, N. (1999) Solving semi-Markov decision problems using average reward reinforcement learning. *Management Science*, **45**(4), 560–574.

Fakih, S.J. and Das, T.K. (2006) LEAD: a methodology for learning efficient approaches for medical diagnosis. *IEEE Transactions on Information Technology in Biomedicine*, **10**(2), 220–228.

Fedson, D.S. and Hant, S. (2003) Pandemic influenza and the global vaccine supply. *Clinical Infectious Deseases*, **36**, 1552–1561.

Fraser, C., Riley, S., Anderson, R.M. and Ferguson, N. (2004) Factors that make an infectious desease outbreak controllable. *Proceedings of the National Academy of Sciences*, **101**(16), 6146–6151.

Gani, R. and Leach, S. (2004) Epidemiologic determinants for modeling pneumonic plague outbreaks. *Emerging Infectious Deseases*, **10**(4).

Gosavi, A. (2004) Reinforcement learning for long-run average cost. *European Journal of Operational Research*, **155**, 654–674.

Halfhill, T. (2006) Inflation Calculator. Available at http://www.halfhill.com/inflation.html, accessed January 2007.

Halloran, M.E., Longini, I.M., Cowart, D.M. and Nizam, A. (2002) Community interventions and the epidemics prevention potential. *Vaccine*, **20**, 3254–3262.

Halloran, M.E., Longini, I.M., Nizam, A. and Yang, Y. (2002) *Containing Bioterrorist Smallpox* (Vol. 298; Tech. Rep. No. 5597).

IOM (2004) *Financing Vaccines in the 21st Century: Assuring Access and Availability* (Tech. Rep.).

Johns Hopkins Bloomberg School of Public Health (2005) MIDAS computer simulation analyzes strategies for stopping flu pandemic grant. Available at http://www.jhsph.edu/publichealthnews/press_releases/2005/cummings_midas.html, accessed November 2006.

Kaelbling, L., Littman, M. and Moore, A. (1996) Reinforcement learning: a survey. *Journal of Artificial Intelligence Research*, **4**, 237–285.

Kaplan, E.H., Craft, D.L. and Wein, L.M. (2002) Emergency response to a smallpox attack: the case for mass vaccination. Available at http://www.pnas.org/cgi/doi/10.1073/pnas.162282799, accessed April 2007.

Longini, I.M., Halloran, M.E., Nizam, A. and Yang, Y. (2004) Containing pandemic influenza with antiviral agents. *American Journal of Epidimiology*, **159**, 623–633.

Longini, I.M. and Hill, A.N. (2003) The critical vaccination fraction for heterogeneous epidemic models. *Mathematical Biosciences*, **181**, 85–106.

Mahadevan, S. (1996) Average reward reinforcement learning: foundations, algorithms, and empirical results. *Machine Learning*, **22**, 159–196.

Meltzer, M.I., Cox, N.J. and Fukuda, K. (1999) The economic impact of pandemic influenza in the United States: priorities for intervention. *Emerging Infectious Deseases*, **5**(5).

Monto, A.S. (2005). Vaccines and antiviral drugs in pandemic preparedness. Available at http://www.cdc.gov/ncidod/EID/vol12no01/05-1068.htm, accessed February 2007.

NAE (2005) Building a better delivery system: a new engineering/health care partnership. Available at http://www.iom.edu/CMS/3809/28393.aspx, accessed May 2007.

NIMGS (2004) Models of infectious disease agent study (MIDAS) project. Available at http://www. jhsph.edu/publichealthnews/press_releases/PR_2004/Burke_MIDAS.html, accessed April 2007.

Patel, R., Longini, I.M. and Halloran, M.E. (2005) Finding optimal vaccination strategies for pandemic influenza using genetic algorithms. *Journal of Theoretical Biology*, **234**, 201–212.

Puterman, M. (1994) *Markov Decision Processes: Discrete Stochastic Dynamic Programming*, Wiley, New York, NY.

Ravulapati, K.K., Rao, J. and Das, T.K. (2002) A reinforcement learning approach to stochastic business games. *IIE Transactions on Scheduling and Logistics*, **36**, 373–385.

US CDC (2006) Preparing for pandemic influenza. Available at http://www.cdc.gov/flu/pandemic/ preparedness.htm, accessed April 2007.

US HHS (2006) HHS pandemic influenza plan. Available at http://www.hhs.gov/pandemicflu/plan/#part1, accessed July 2006.

US HHS (2007) Pandemic flu: planning and response activities. Available at http://www.pandemicflu.gov/ plan/, accessed March 2007.

WHO (2004) World Health Organization: influenza. Available at http://www.who.int/mediacenter/factsheets/2003/fs211/en/, accessed September 2007.

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