J Med Syst (2011) 35:1465–1475
DOI 10.1007/s10916-009-9423-1

ORIGINAL PAPER

A Generic Simulation Model to Manage a Vaccination Program

Arben Asllani · Lawrence Ettkin

Received: 14 September 2009 / Accepted: 16 December 2009 / Published online: 29 January 2010

Abstract The main purpose of this paper is to demonstrate how a computer model can be used as a decision making tool regarding vaccination programs. These programs include vaccination against traditional influenza, avian influenza, H1N1 (swine flu), or other diseases. Specifically, the proposed simulation model is used to investigate the impact of herd immunity, to estimate the vaccination rate for which a given disease is placed into an endemic state, and to calculate the overall cost of a vaccination program from a societal perspective. In addition, the tool can help to define an optimal vaccination rate which will result in the minimum overall cost for a vaccination program. The paper demonstrates several advantages of simulation over other decision making methods. Simulation is used to "mimic" the behavior of the disease, test a range of alternative solutions for different scenarios, and to finely adjust the model and reflect possible vaccination scenarios.

Keywords Vaccination program · Computer simulation · Herd immunity · Vaccination cost

Introduction

A recent study from the University of Warwick suggests that the best way to control the current H1N1 flu pandemic is to target children and vaccinate them using the limited supplies of available vaccines [14]. The study concludes that due to "herd immunity effect" vaccinating children would offer protection to unvaccinated adults. In this paper, we offer a simulation model which can be used by healthcare practitioners as a decision making tool to investigate the impact of herd immunity, estimate the best possible vaccination rate, and minimize the cost of the vaccination program. The proposed simulation based template is universal and can be used for any given vaccination scenario. The model allows the decision makers to select a disease and its appropriate reproduction number, i.e. how many people are normally infected by one infected person. In addition, the decision maker can estimate the time required to transmit the disease from one person to another, the cost of the vaccine, the cost of treatment, and so on.

Once the specific vaccination scenario is created, the proposed computer model can be used to suggest the best courses of action with respect to a vaccination program. We illustrate our approach by creating a hypothetical scenario using the ProModel®, a simulation package created by ProModel Corporation. However, other simulation tools, including those which are MS Excel-based may be used. Regardless of the software used, the conceptual and logical design of the proposed vaccination model is based on the existing theory of vaccination models as described in the following section.

Theory of vaccination

The proposed simulation model is based on the existing theory of vaccination. Such theory was developed more than 100 years ago, when Lotz [13] developed a basic mathematical model to clarify the impact of a vaccination program. He offered two important theoretical concepts in infectious disease epidemiology: basic reproduction number and herd immunity. The concept of basic reproduction number is

A. Asllani (✉) · L. Ettkin
Department of Management,
University of Tennessee-Chattanooga,
Chattanooga, TN 37403-2598, USA
e-mail: beni-asllani@utc.edu

further explored [2, 9] and indicates the average number of secondary cases arising from the introduction of an initial case. Herd immunity is the population-level consequence of acquired immunity among certain individuals which will reduce the risk of acquiring infection among susceptible individuals. One major goal of a vaccination program is to take advantage of herd immunity. To further describe the dynamics in the generation of new cases, the literature also suggests the so called "generation interval" or the "serial interval," which represents the mean time interval between onset of initial case and onset of secondary cases [3, 9, 10].

Anderson and May [1]; Diekmann and Heesterbeek [9] came very close to determining the required vaccination coverage for eradication using a randomly mixing population. Based on this research, many models that predict the impact of vaccination programs have been developed. These models can be grouped into two categories: dynamic and static. The major difference between these types is that dynamic models capture the indirect protection resulting from immunization, i.e. herd immunity effect. Static models simply omit this. Currently, most economic evaluations of vaccination programs use static models [7].

In recent years, several new methodologies have been introduced. Examples of methodological choices are type of analysis (cost-benefit, cost-effectiveness, or cost-utility), the perspective (societal or payer), valuation technique (willingness to pay, standard gamble, multi-attribute utility scores), and discount rates [5, 6]. Additionally, recent literature shows many models with parameter uncertainties [8]. Uncertainties include parameters such as biological, demographic, epidemiological, medical, and economic.

The objective functions in other proposed models vary from the willingness-to-pay method to cost-benefit analysis [4]. However, the literature suggests that in spite of the measure, it is very important that proposed models are consistent with a coherent theory of the health condition [17]. In lieu of such requirements, many disease and population specific studies are conducted to investigate the impact of vaccination rate on the cost of a vaccination [15, 16].

This paper uses the mathematical foundations of the vaccination theory to design a complex, yet practical, simulation model. The proposed model is dynamic, because it considers the herd immunity effect. It is also stochastic, because many input variables, such as reproduction number, transmission period, event outcomes, treatment costs, are random variables generated using well defined statistical distribution functions.

The vaccination process model

When an infection arrives in a susceptible population, the disease is spread based on the reproduction number and immunization rate. Figure 1 shows that people who are infected can either self-recover, seek physician help, or go to the emergency room (ER). The physician or the ER doctor will provide the necessary treatment. In more serious cases, the patient may require hospitalization. After the hospital treatment, patients recover and, in rare cases, the model assumes that some patients will not recover.

In our model, we simulate arrivals of infected people in the "susceptible people" section in Fig. 1. This is a stochastic feed. R_o is simulated as a random variable the time between arrivals of the new set of infections is a random variable. We also assumed it to be exponential with a mean R_p, where reproduction period R_p represents the expected time to transmit the disease from one person to another. Once people are infected and moved to "sick people" section of our simulation model, there are three potential outcomes: self-recovered, physician visit, or emergency room. Our model assigns probabilities for each of the above three options. Such probability values depend on the type of decease and population profile, such as age, insurance coverage, income level, and so on. Further, we assume that the above three events are both collectively exhaustive and mutually exclusive. Collectively exhaustive property requires that when a person is infected, at least one of the events must occur: the person must either self-recover, see a physician, or visit the ER. Mutually exclusive property requires that occurrence of any of the three events automatically implies the non-occurrence of the remaining two events: the infected person cannot self recover and see a physician for the same infection, or cannot see a physician and visit the ER at the same simulation scenario.

Once a patent has received medical assistance through a physician or through ER, he or she will have two possible outcomes: recovered or hospitalized. These two events are also collectively exhaustive and mutually exclusive. Probabilities for each of these two options are assigned based on the historical data of the disease under investigation. We assume that once patients are physically recovered or self-recovered, they cannot become infected again, as such the number of susceptible people is also reduced accordingly.

Hypothetical example

We illustrate our computer simulation model with a hypothetical example. Let us suppose that the healthcare department of a local county (HDC) is trying to identify optimal vaccination policies for the upcoming season for disease X. X can be traditional influenza, H1N1 (swine flu), or any other disease where a vaccination program is recommended. The county has about 10,000 school-age

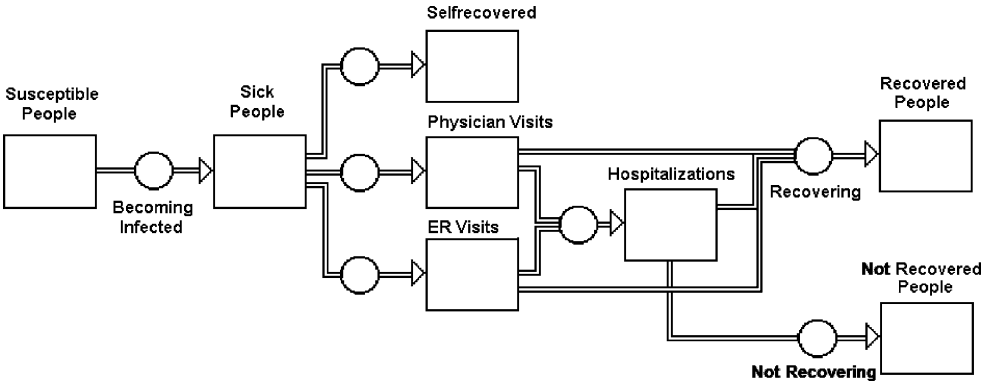

Fig. 1 Basic scenario for simulation model

children (under 18 years old) who can potentially receive the vaccine. The major goal of the program is to determine an appropriate vaccination rate in hopes of reducing the overall cost of the disease. HDC believes that the vaccination rate can be controlled by covering different amounts of the cost for the vaccine. HDC has compiled Table 1 which shows the relationship between HDC payment level and the vaccination rate based on the records from the last few years assuming a base cost for the vaccination of $60 per each dose. We assume that the total cost of the vaccination program is a function of the vaccination rate. As will be demonstrated, our model will calculate the total treatment cost and use this information when identifying the optimal vaccination rate.

Simulation model variables

Data shown in Table 2 can be estimated based on transaction records of HDC. Using Stat:Fit®, a components of ProModel®, we can generate statistical distributions using a series of observed data. Actual values used in the model, as well as statistical distributions are shown in the last column of Table 2.

The variables described in Tables 2 and 3, are grouped into three classifications: controlled variables, decision variables, and the objective function. The first set, controlled variables are used to design a simulation scenario. The other two sets, decision variables and the objective function are used to optimize a simulation scenario. The decision maker's question is: what is the level of the decision variable for which the objective function is best or optimized?

Table 1 Cost of the vaccine for HDC and vaccination rate

Cost of vaccine to HDC	Vaccination rate
$0–$3	10%
$3–$12	20%
$12–$24	40%
$24–$36	50%
$36–$48	60%
$48–$60	80%

Obviously, the higher the vaccination rate, the more people are vaccinated, and the less people are infected. However, the answer to this question becomes more difficult when considering the "herd immunity" effect. As such, we will also use the simulation model to calculate the level of vaccination rate which will trigger the "herd immunity." While the answer to this question is mathematically provided for deterministic models [11], our simulation investigates "herd immunity" in a stochastic environment, which is more realistic for disease scenarios.

Running the simulation model

As shown in Appendix A, to initiate the simulation model, the decision maker is prompted to answer questions about the size of the population, expected reproduction number, the vaccination rate, expected time to transmit the disease from one person to another, and cost of the vaccine. The answers to the above obviously depend on the type of disease and population segment being investigated. Each answer set allows the decision maker to identify a given scenario. After each scenario is created, the simulation is run using an appropriate number of replications allowing for statistically significance results. Harrell et al. [12] provides an approach to computing the number of replications required to ascertain a selected degree of accuracy. In our example, each scenario is replicated 100 times to ensure data reliability. Figure 2 shows a snapshot of the simulation model in progress.

There are three main areas of the simulation: decision model display, data display, and graphical display. First, the decision model display is similar to the vaccination scenario shown in Fig. 1. However, when the model is running, the decision maker is able to see dynamic, run-time interface data. At any time during the simulation run, the model will display the number of infected patients, number of patients who are seeing a doctor, are hospital-

Table 2 Major input variables of vaccination model

Variable name	Description	Notation in the model	Random	Value in the model
Population size	Number of people subjected to a vaccination program.	*Pop_Size*	No	10,000
Reproduction ratio	Average number of people infected by one infected person.	R_o	Yes	Uniform U(4, 1) people
Reproduction period	Expected time to transmit the disease from one person to another.	*R_period*	Yes	Exponential E(5) days
Wait until doctor	Average time people wait sick until they decide to see a doctor in hope of self-recovery	*W_until_dr*	Yes	E(2) days
Wait until recovered	Average time people have to wait until they are considered recovered	*W_until_re-covered*	Yes	E(5) days
Cost of vaccine	The cost to buy and administer a single vaccine	*Vaccine_C*	No	$60
Physician cost	Cost paid to a physician for a single visit	*Physician_C*	Yes	Uniform U(120, 20)
Hospital cost	Cost paid for a single hospitalization case	*Hospital_C*	Yes	Uniform U(480, 50)
ER cost	Cost paid for a single visit in the ER	*ER_C*	Yes	Uniform U(240, 50)

ized, self-recovered, and recovered. Second, the data display (in the lower right side of the screen) shows dynamic data of the model outcomes. As shown, the decision makers can trace results about model parameters, simulation results, and cost results. Third, the graphical display (in the lower left side of the screen) shows dynamic plots of vaccination rate and number of infections. The graph allows the decision maker to visually see the effects of assigning different vaccination rate. Since each scenario is run 100 times, the simulation engine will determine the mean and standard deviation for each variable. The data generated by the model can be further analyzed to fine tune the model and the decisions resulting from the model.

Validating herd immunity

If we denote the initial number of infections by a, the reproduction number by R_o, and the generation number by n, the number of infections increases according to the series a, aR_o, aR_o^2, aR_o^3, ..., aR_o^n. Starting with a single initial infection, the number of cases in the n^{th} generation is equal to the reproduction number (R_o) to the power of n. This exponential growth represents the behavior of the disease when there is no presence of herd immunity. However, as the disease progresses from one generation to the next, the infected people are no longer susceptible to the disease. As such, the infection ratio or the number of people infected in the next generation from a single case can be calculated as:

$$I_n = I_{n-1} R_o \frac{S_{n-1}}{P}$$

where:

I_n	number of people infected in generation n
R_o	reproduction number for a given disease and population group
S_{n-1}	number of susceptible individuals in generation $n-1$
P	size of population group

Table 3 Major decision and derived variables of simulation model

Variable	Description	Notation in the model	Type
Vaccination rate	Percentage of population vaccinated before the simulation starts. Several values are used to illustrate different scenarios as well as herd immunity effect.	*V_rate*	Decision variable
Number of infections	Number of people who are infected.	*Infected*	Derived value
Immunized	Number of people vaccinated before the simulation starts.	*Immunized*	Derived value
Recovered	Number of people infected and recovered or self-recovered	*Recovered*	Derived value
Total vaccination cost	Total cost of vaccination program. Calculated as a product of number of people being vaccinated times the portion of cost covered by HDC	*Vaccination_C*	Derived value
Total treatment cost	Total cost of treatment. Calculated as a sum of physician cost, hospitalization cost, and ER cost	*Treatment_C*	Derived value
Total cost	Total cost of the disease. Calculated as a sum of total vaccination cost and total treatment cost. Goal is to minimize this.	*Total_C*	Derived value

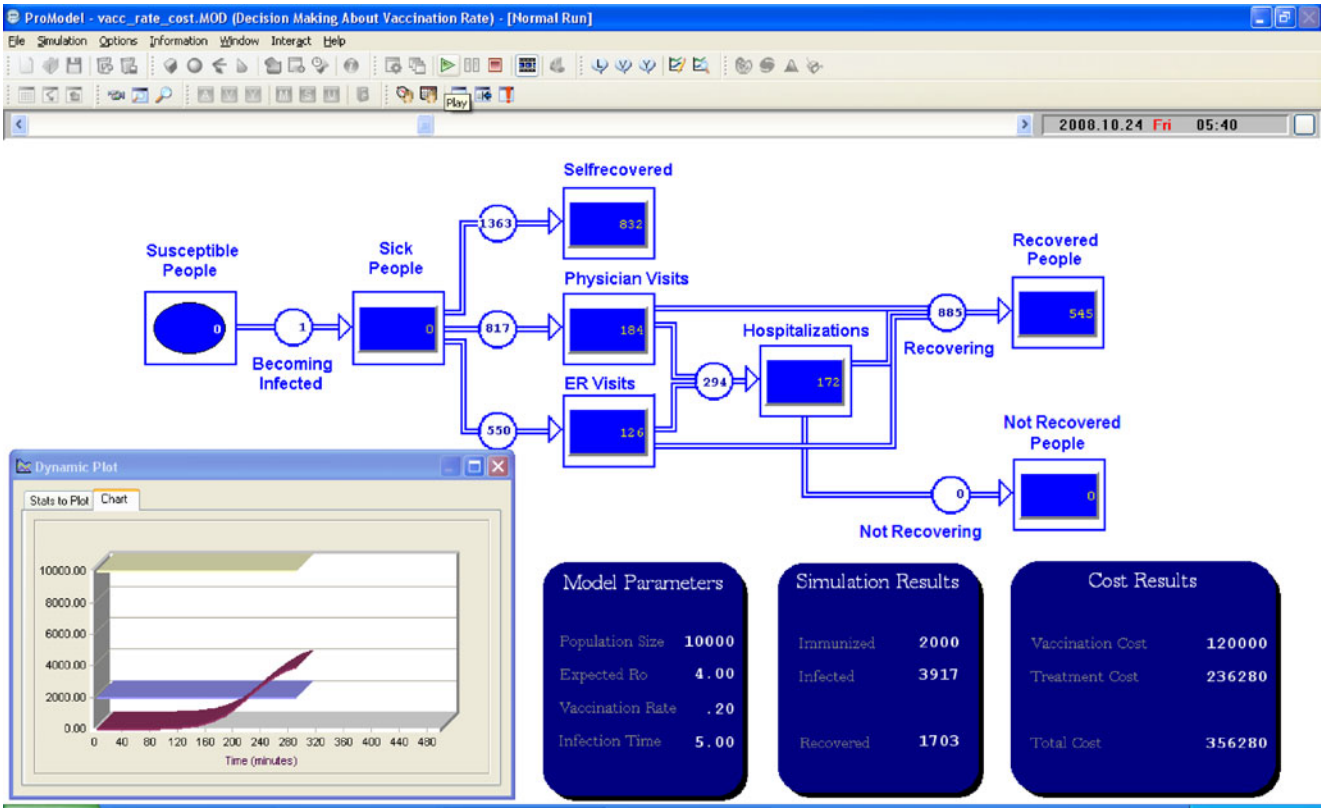

Fig. 2 Simulation model in progress

The above formula represents the behavior of the disease when herd immunity is present. As time passes and n increases, S_{n-1} decreases and so does the number of people becoming infected I_n. Validating herd immunity was an important part of our model validation. As shown in Fig. 3, we compared two alternatives: (a) scenario model with herd immunity using the above formula and (b) scenario model where herd immunity is purposefully suppressed.

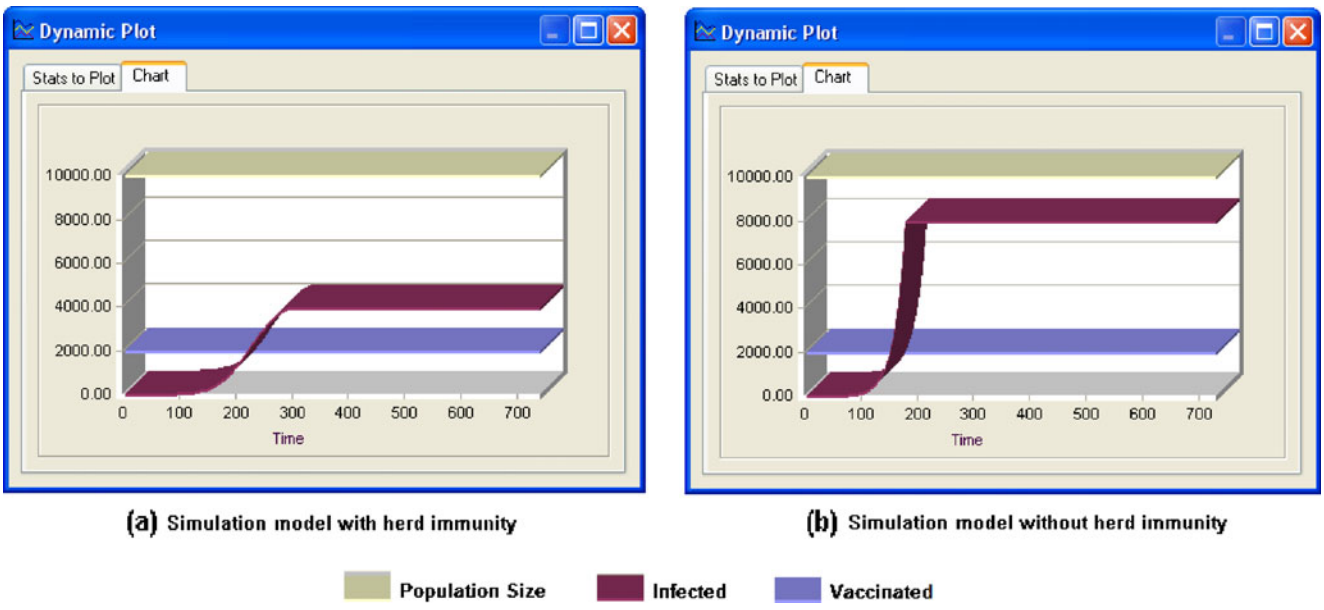

Fig. 3 Impact of herd immunity on the number of infections

As shown in Fig. 3(a), in a given scenario when vaccination rate is selected to be 20%, the infection of population increases until 40% of the population is infected. After that point, herd immunity will not allow the spread of further infections. In Fig. 3(b) where herd immunity effect is removed and the same vaccination rate of 20% is applied, infection will continue to spread until 80% are infected. This analysis re-enforces the validity of the model and shows the power of computer simulation as a decision making tool. The decision maker is able to evaluate IF-THEN scenarios which would be difficult if not impossible to generate in a real environment.

Impact of vaccination rate on the number of infections

Without cost considerations, the decision maker might be interested in defining what percentage of the population needs to be vaccinated so the number of infected is kept under a certain level. Our proposed simulation model can also be used to investigate the impact of different vaccination rates on the number of infections. Figure 4 shows four different scenarios based on different vaccination rates.

Scenario (a) has no previous immunization program so the vaccination rate is 0%. As shown, 60% of the population is infected and then herd immunity starts to impact the spread of the disease. Due to herd immunity, scenario (b) with an immunization rate of 20% will have 40% of population infected, scenario (c) with an immunization rate of 40% will have 20% of population being infected, and scenario (d) with an immunization rate of 60% will not have anyone else infected.

Using the above results, decision makers can identify the portion of population that needs to be immunized so the impact of herd immunity can be used. Importantly,

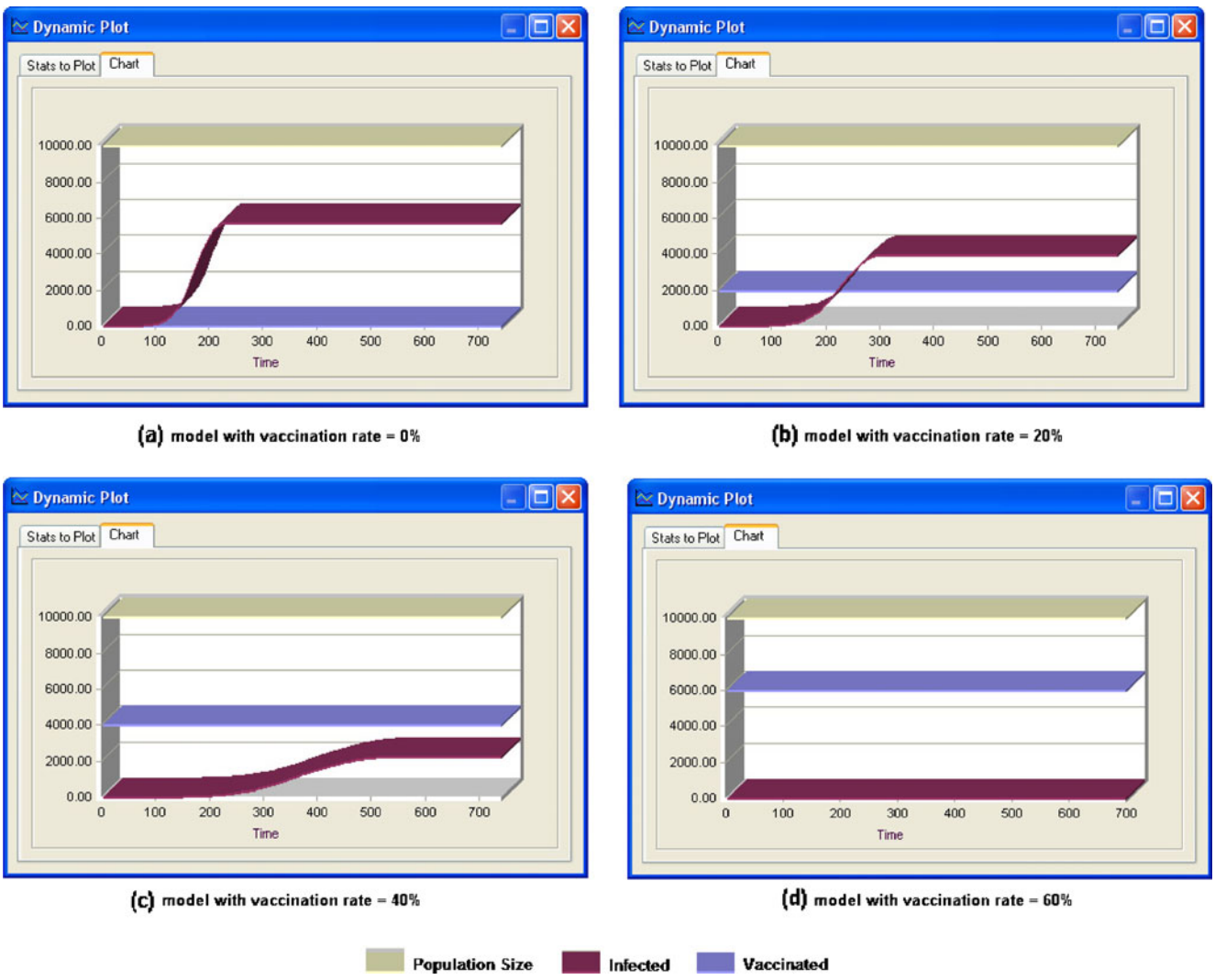

Fig. 4 Comparison of different vaccination rates

the decision maker needs to know the vaccination rate which will keeps the disease under control. This rate is defined based on medical considerations. However, the acceptable level is often defined based on the cost of vaccination and cost of treating the disease.

Vaccination rate and the cost of vaccination

The model can also be used to investigate the impact of different vaccination rates and the overall cost of the treatment of a disease. Further, the proposed simulation template can be used to identify the optimal immunization or vaccination rate which minimizes the overall cost. The total costs included in the model are shown in Fig. 5 and consist of vaccination costs and treatment costs. As mentioned earlier, vaccination costs represent the cost of a single vaccine for HDC (the maximum possible value or the upper limit as shown in Table 1) multiplied by the number of people being vaccinated. In general, the lower the cost of a single vaccine, the more people will be vaccinated. Treatment costs are randomly generated by the model and include total physicians, emergency visits costs, and hospitalizations costs.

As shown in Fig. 5, there is a certain vaccination rate (60%) which minimizes the overall cost. Using the data in Table 1, HDC can achieve a 60% vaccination rate by offering to cover $36–$48 per vaccine. Any higher vaccination rate will not reduce the overall cost of the disease, mainly due to herd immunity effect. In such case, reduction in the cost of treatment (because more people will be vaccinated) is not justified because the vaccination cost will be higher. Any lower vaccination rate will result in a lower vaccination cost however the cost of treatment will be higher. So we conclude that it is not necessary for the HDC to offer any higher coverage in the vaccination cost. We must note that this is just a hypothetical example provided here to illustrate the kind of analysis that can be performed by our model.

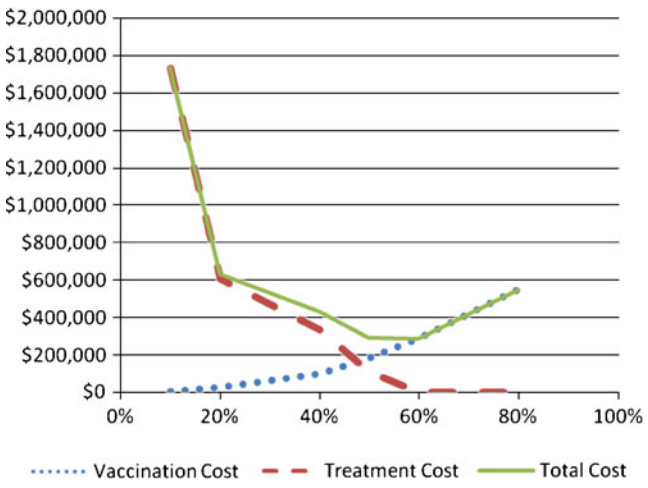

Fig. 5 Relationship between vaccination rate and total cost

Conclusions

This paper proposes a simulation model which can be applied to any vaccination program. The model can be used by healthcare practitioners as an effective decision making tool to identify an appropriate vaccination rate based on medical and cost-based considerations. The model can also be used to study the impact of herd immunity on the vaccination program. The proposed model is illustrated with a hypothetical example from the perspective of a healthcare department.

It has been found that simulation has several advantages over mathematical or other decision making methods. Simulation uses a logical abstraction of the reality through a computer model that "mimics" the behavior of the disease as it arrives in a given population target. Once the computer based simulation model is validated, the decision maker can test a range of alternative solutions for different disease scenarios. Another advantage of the proposed model is its flexibility. The decision maker is able to recreate scenarios for a certain disease, a given population target, and different vaccination rates.

As a final note, one should remember that a simulation model is only as good as the assumptions on which it is based. If a model makes predictions which are out of line with observed results, one must go back and change our initial assumptions in order to make the model useful. In future studies, we intend to incorporate other costs, such as parental time lost, expected costs of rehabilitation, and long term care associated with permanent disabilities.

Appendix A: Similation code

```
   ************************************************************************
                  USING PROMODEL FOR VACCINATION PROGRAM
   ************************************************************************

This model simulates a vaccination program and is designed to assist you
in the process of deciding the best vaccination rate in order to keep a
disease under control and minimize the overall the cost of a given
disease. The model also illustrates the impact of "herd immunity",
endemic, and epidemic states.

This is a general template and can be customized for a specific decease,
population group, disease reproduction number, and reproduction period.
You will be able to test several scenarios with different vaccination rate
and see the impact on the disease control.

************************************************************************
  Initialization Logic:              animate 40
                                     infected = 1
                                     immunized = POP_size*v_rate
                                     Vaccination_C = immunized*Vaccine_C

                                     activate Sub_DP
                                     activate Sub_setup
************************************************************************
* Locations                                    *
************************************************************************

Name                Cap      Units Stats       Rules      Cost
------------------ -------- ----- ----------- ---------- ------------
Susceptible_people POP_SIZE 1     Time Series Oldest, ,
Sick_people        POP_SIZE 1     Time Series Oldest, ,
Self_recovered     POP_SIZE 1     Time Series Oldest, ,
Physician_visit    POP_SIZE 1     Time Series Oldest, ,
ER_visit           POP_SIZE 1     Time Series Oldest, ,
Hospitalization    POP_SIZE 1     Time Series Oldest, ,
Recovered_people   POP_SIZE 1     Time Series Oldest, ,
Deceased_people    POP_SIZE 1     Time Series Oldest, ,
************************************************************
* Entities                                   *
************************************************************
Name          Patient    150          Time Series
************************************************************
************************************************************
Processing                                  *
************************************************************
Process                          Routing

Entity   Location      Operation      Output   Destination   Rule
-------- ------------------ ------------------   ---- -------- -------
Patient
Susceptible_people Wait E(w_until_dr)day
                                  Patient  Sick_people      FIRST 1
Patient  Sick_people
If (Pop_size-immunized-infected)>0
Then
Begin
newly_infected = U(RO,1)*((Pop_size-immunized-recovered-
infected)/Pop_size)
```

```
Order newly_infected patient to Susceptible_people
infected = infected + newly_infected
Route 1
End
else Route 2
          Route 1       Patient  Self_recovered
                        0.500000 1
                        inc recovered
                        inc self_recovered_P
                        Patient  Physician_visit
                        0.300000
                        inc seeing_dr_P
                        Patient  ER_visit
                        0.200000
                        inc ER_P
             Route 2    Patient  EXIT    FIRST 1

Patient
Self_recovered   wait E(W_until_recovered)day
                     Patient  EXIT             FIRST 1
Patient
Physician_visit  wait E(1) day
T_Physician_C = T_Physician_C+U(Physician_C,20)

                        Patient  Recovered_people
                        0.800000 1
                        inc recovered_P
                        Patient  Hospitalization
                        0.200000
                        inc hospital_P
Patient
ER_visit   wait E(1) day
           T_ER_C = T_ER_C+U(ER_C,50)

                        Patient  Recovered_people
                        0.600000 1
                        inc recovered_P
                        Patient  Hospitalization
                        0.400000
                        inc hospital_P
Patient
Hospitalization  wait E(3) day
T_Hospital_C = T_Hospital_C+U(Hospital_C,50)
                        Patient  Recovered_people
                        0.990000 1
                        inc recovered_P
                        Patient  Deceased_people
                        0.010000
                        dec POP_SIZE
                        inc dying_P
Patient
Recovered_people   wait E(W_until_recovered) day
inc recovered
Treatment_C = T_physician_C + T_ER_C + T_hospital_C
Total_C = Vaccination_C + Treatment_C
                        Patient  EXIT      FIRST 1
Patient Deceased_people
accum infected
                        Patient  EXIT      FIRST 1
```

```
*********************************************************************
*                        Arrivals
*********************************************************************

Entity   Location       Qty Each   First Time Occurrences
-------- ---------- ---------- ----------- ---------- ------------
Patient  Susceptible_people 1          0          1

*************************************************************************
*                              Variables (global)
*********************************************************************
 ID                Type         Initial value Stats
----------------- ------------ ------------- -----------
  POP_SIZE          Integer      10000         Time Series
  RO                Real         4             Time Series
  infected          Integer      0             Time Series
  recovered         Integer      0             Time Series
  immunized         Integer      0             Time Series
  v_rate            Real         1             Time Series
  R_period          Real         5             Time Series
  W_until_dr        Integer      2             Time Series
  hospital_time     Integer      3             Time Series
  W_until_recovered Integer      4             Time Series
  newly_infected    Integer      1             Time Series
  self_recovered_P  Integer      0             Time Series
  recovered_P       Integer      0             Time Series
  seeing_dr_p       Integer      0             Time Series
  ER_P              Integer      0             Time Series
  hospital_P        Integer      0             Time Series
  dying_P           Integer      0             Time Series
  Susceptible_P     Integer      0             Time Series
  Vaccine_C         Integer      60            Time Series
  Vaccination_C     Integer      0             Time Series
  Physician_C       Integer      120           Time Series
  ER_C              Integer      240           Time Series
  Hospital_C        Integer      480           Time Series
  Treatment_C       Integer      0             Time Series
  Total_C           Integer      0             Time Series
  T_Physician_C     Integer      0             Time Series
  T_Hospital_C      Integer      0             Time Series
  T_ER_C            Integer      0             Time Series


*********************************************************************
*                                 Subroutines
*********************************************************************

  ID         Type   Logic
  ---------- ------------ ---------- ------------
  Sub_DP     None   WAIT 4 HR
DYNPLOT "Immunization Versus Infection Rate"

PROMPT "Please enter the expected size of population:",POP_SIZE
PROMPT "Please enter the expected reproduction number:",RO
PROMPT "Please enter vaccination rate:",v_rate
PROMPT "Please enter time to transmit the disease:", R_period
PROMPT "Please enter the cost of the vaccine:", Vaccine_C

*********************************************************************
*                  END
*********************************************************************
```

References

1. Anderson, R. M., and May, R. M., Directly transmitted infectious diseases: control by vaccination. *Science* 215:1053–1060, 1982.
2. Anderson, R. M., and May, R. M., *Infectious diseases of humans: dynamics and control*. Oxford University Press, New York, 1991.
3. Bailey, N. T. J., *The mathematical theory of infectious diseases and its applications*, 2nd edition. Griffin, London, 1975.
4. Birch, S., Gafni, A., and O'Brien, B., Willingness to pay and the valuation of programmes for the prevention and control of influenza. *Pharmacoeconomics* 16(Suppl 1):55–61, 1999.
5. Briggs, A. H., and Gray, A. M., Handling uncertainty when performing economic evaluation of healthcare interventions. *Health Technol. Assess.* 3:1–134, 1999.
6. Briggs, A. H., Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics.* 17:479–500, 2000.
7. Brisson, M., and Edmunds, W. J., Economic evaluation of vaccination programs: the impact of herd immunity. *Med. Decis. Mak.* 23:76–82, 2003.
8. Brisson, M., and Edmunds, W. J., Impact of model, methodological, and parameter uncertainty in the economic analysis of vaccination programs. *Med. Decis. Mak*. 434–446, 2006.
9. Diekmann, O., and Heesterbeek, J. A. P., *Mathematical epidemiology of infectious diseases: model building, analysis and interpretation*. Wiley Series in Mathematical and Computational Biology, New York, 2000.
10. Fine, P. E., The interval between successive cases of an infectious disease. *Am. J. Epidemiol.* 158:1039–1047, 2003.
11. Garnett, G. P., Role of herd immunity in determining the effect of vaccines against sexually transmitted disease. *J. Infect. Dis.* 191 (Suppl 1):S97–106, 2005.
12. Harrell, C. R., Bateman, R. E., Gogg, T. J., and Mott, J. R. A., *System Improvement Using Simulation, (3rd Ed.)* Orem, UT. PROMODEL® Corporation, 1995.
13. Lotz, T., *Pocken and vaccination. Bericht über die Impffrage, erstattet im Namen der schweizerischen Sanitatskommission an den schweizerischen Bundersrath. Benno Schwabe,* Verlagsbuchhandlung, Basel (in German), 1880.
14. Reuters.com, Vaccinate Kids to Control H1N1 Flu, Retrieved from http://www.reuters.com/articlePrint?articleId=USLI88962120090618 on Sept. 3, 2009
15. Sewell, E. C., and Jacobson, S. H., Using Monte Carlo simulation to determine combination vaccine price distributions for childhood diseases. *Health Care Manage. Sci.* 5(2):135–145, 2002.
16. Sewell, E. C., and Jacobson, S. H., Using an integer programming model to determine the price of combination vaccines for childhood immunization. *Ann. Oper. Res.* 119(1–4):261–284, 2003.
17. Weinstein, M. C., O'Brien, B., Hornberger, J., et al., Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR task force on good research practices—modeling studies. *Value Health* 6:9–1, 2003.