

Simulation as Decision Support in Pandemic Influenza Preparedness and Response

Johan Jenvald

VSL Research Labs
Linköping, Sweden
johan.jenvald@vsl.se

Magnus Morin

VSL Research Labs
Linköping, Sweden
magnus.morin@vsl.se

Toomas Timpka

Dept. of Social Medicine and Public Health,
Linköping University,
Linköping, Sweden
tti@ida.liu.se

Henrik Eriksson

Dept. of Computer and Information
Science, Linköping University,
Linköping, Sweden
her@ida.liu.se

ABSTRACT

Outbreak of a destructive pandemic influenza threatens to disrupt societies worldwide. International agencies and national governments have prepared plans and recommendations, but it is often decision-makers with the local authorities that are responsible for implementing the response. A central issue for these decision makers is what interventions are available and effective for the specific local community. The paper presents a simulator architecture and its relation to a workflow for decision support in influenza preparedness and response. The simulator can simulate pandemic scenarios, using localized community models, in the presence of various interventions to support an evaluation of potential response strategies. The architecture includes a customized modeling tool, separated from the simulation engine, which facilitates swift scenario modification and recalculation. This flexibility is essential both to explore alternative solutions in planning, and to adapt to changing requirements, information, and resources in outbreak response. An example simulation, based on actual population data from a reference city, illustrates the approach.

Keywords

Modeling, simulation, pandemic influenza, decision support, local community, workflow, preparedness, response.

INTRODUCTION

An outbreak of pandemic influenza can have severe effects on society. With a large proportion of the population disabled by severe infections, vital functions and infrastructure may be at risk and fundamental services may be disrupted. This threat has generated preparatory actions on both international and national levels. Internationally, the World Health Organization (WHO) has taken initiative to plans, instructions and recommendations on how to manage an outbreak of pandemic influenza. On the national level, governments have developed policies and plans, based on WHO's recommendations, for managing outbreaks and have adapted legislation to deal with the threat. Local authorities are responsible for planning and implementing interventions in case of an actual outbreak, considering both national policy and local conditions.

Decision makers at all levels are expected to take action to minimize the consequences of the pandemic, but they face serious problems that may impede an effective response. Limited supplies force decision makers to determine how and when to distribute the available doses of anti-viral medicine and vaccine; alternative strategies must be considered. Incomplete information about the virus transmission characteristics and the effectiveness of different medicines makes intervention planning hypothetical until further information becomes available during the pandemic. Information delays in the surveillance and reporting system will make it difficult to deduce the actual status of the outbreak from the reports available; alternative situations have to be considered in parallel. Insufficient attention to local conditions may lead to ecological fallacy; that is, results obtained at regional or national levels may not necessarily be congruent with the local levels, because regional averages may mask diversity between smaller areas (Meade & Earickson, 2005). Age distribution of the population, school structure, and infrastructure, together

with social and economical conditions, affect how the disease will spread in the local community. A decision support system can help the decision maker overcoming these problems in the planning and response process.

Forecasting is an essential component in a decision support system for preparing for and responding to pandemic influenza outbreaks. Different simulation models have been developed in order to predict the outcome of influenza outbreaks in the presence of various interventions (Longini et al., 2004; Longini et al., 2005; Ferguson et al., 2006; Germann et al., 2006). However, these simulations have important limitations with respect to the decision makers' needs. They have been designed to answer general questions in a research setting. They do not support the rapid formulation, variation, modification and recalculation of outbreak scenarios that is necessary to evaluate alternative intervention strategies in a situation with uncertain information. Instead, modifications require time-consuming and error-prone programming. We argue that a workflow for simulation-based decision support must incorporate a different type of simulator architecture, specifically designed to facilitate the exploration of alternative intervention strategies under hypothetical but variable conditions.

In this paper, we present an architecture for simulating influenza outbreaks and describe its relationship to the decision-making workflow in local institutions having responsibility for a pandemic response. A key feature is the separation of modeling and model execution, combining an ontology-based modeling environment with a customized simulator capable of interpreting and executing the models constructed. This separation makes it possible to bring modeling closer to the decision maker, thus facilitating scenario formulation and modification, while retaining computational efficiency. We illustrate our approach with the simulation results from a reference local community.

The paper is organized as follows. We describe the decision problem at hand and its dynamic progress during a pandemic influenza outbreak. We then provide an overview of aspects of influenza modeling and simulation followed by our architecture and implementation. Finally, we present our simulation results and discuss them in relation to the local-level decision-support challenges in case of a pandemic outbreak.

PREPARING FOR RESPONSE TO PANDEMIC INFLUENZA

Understanding the problem of managing a pandemic starts with understanding the multitude of different societies. For example, there may be significant differences in the spread of a disease in a rural area with low level of commuting compared to a major urban area with an extensive public transportation system. There may also be differences in social structure and age distribution of the population, which can have considerable impact on the spread of the disease. Therefore, local decision makers have to decide on what interventions to apply or activate. Certain interventions may not be available or applicable for the specific community. Others may have little or no effect on the spread of the disease.

All interventions have a cost for society. An important question is when to activate a particular intervention and how long to keep it active. In today's world—characterized by transcontinental logistics and the just-in-time delivery of food, goods and people—a local outbreak may become a global pandemic in a few weeks. This situation introduces another question: if the decision maker activates an intervention, when and how is it possible to evaluate its effects? These questions are example of issues to take into account in the preparedness and response process.

Preparedness and response process

A systematic preparedness and response process has a cyclic nature, as depicted in Figure 1. Evaluating the situation to define risks, vulnerabilities, needs, and resources is the natural first step, which provides the input to the planning step. The evaluation gives a baseline for exploring and preparing suitable interventions that can be put in place in case of an outbreak. Evaluation and planning can be conducted before an outbreak, but some aspects of the illness and its effects may not be known, so the resulting plan must be considered incomplete and hypothetical. In a dynamic world, changing conditions and new knowledge can invalidate the plan. It is therefore necessary to repeat the evaluation at regular intervals to ensure that the plan is current or, alternatively, to specify what aspects of the plan that need modification.

Exercises give opportunities to test plans and train key personnel in a controllable and safe environment. Exercises can inform evaluation and planning, for example by revealing areas that are not covered or parts of the plan that are not viable. In addition to preparing key personnel, regular exercises are an excellent source of information for identifying improvements needed in the response organization and in plans and instructions. Incorporating these lessons in evaluation and planning is essential.

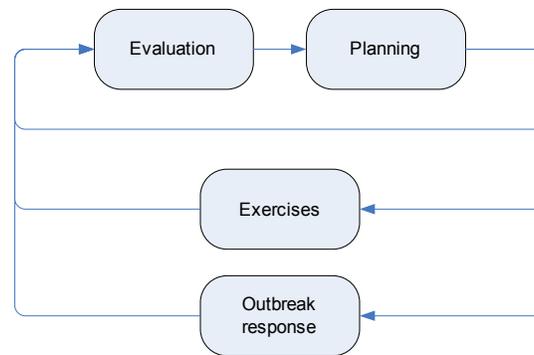


Figure 1: Preparedness and response cycles

The ultimate test of preparedness is an actual outbreak. Decision makers must analyze the situation, taking resources and information into account, explore alternative courses of action and adapt the plan accordingly. Again, the experience accumulated in the response can provide invaluable feedback for preparing for the next outbreak.

Intervention planning

Managing an influenza outbreak is a dynamic decision-making task (Brehmer, 1992). In such a task, a series of interdependent decisions is required to reach the defined goal in an environment where the state of the decision-problem changes, both spontaneously and as a result of the decision-maker's actions. As a consequence, dynamic decision-making must be treated as an ongoing, real-time process striving to control an emerging situation. Interventions are the control mechanisms at the decision maker's disposal.

Interventions affect the dynamics of the disease in three principle ways: (1) by reducing the probability of transmission in contacts between infected and susceptible people, (2) by reducing the number of contacts, and (3) by shortening or eliminating the duration of the infectious phase. Depending on the type of interventions, the intervention model modifies the transmission and mixing parameters accordingly.

Medical interventions such as treatment with anti-viral medicine and vaccination reduce transmission probabilities and shorten the time of illness. Limitations in the number of doses available make it necessary to prioritize among potential receivers. Targeting school children may decrease the number new influenza cases by reducing the transmission probability. On the other hand, targeting elderly people may reduce the number of fatalities in that group by shortening the duration of the infectious phase. Which is more desirable?

Closing schools is an intervention that reduces the number of contacts in a particular population group. On the other hand, school children who are not at school require attention at home, which may pull mothers and fathers from the workforce, thus causing problems in other parts of society.

When selecting interventions, the time to implement them and the time until they give effect must be taken into account. For example, vaccination can provide good protection, but it takes time to vaccinate a full population. Also, the durability of the intervention at hand is important to consider. Anti-viral prophylaxis, for example, is only protective as long as you take the medicine. When you are out of medicine, you have no protection. Some interventions cannot be exhausted, and can be used again, such as closing schools and airports. They can, however, instead have severe social and economical consequences.

Given presumably incomplete information about cases, decision-makers need to be able to make a best estimate of the projected disease situation. They need to assess the current situation; forecast future morbidity given the particular structure and population of the local community; identify and implement effective interventions; and monitor the effectiveness of interventions that are put in place. Before the actual disease outbreak, policies and guidelines have to be developed specific to the social structure and population characteristics of the local community. Prediction of the number and distribution of cases in the local community under various intervention programs can here be proactively computed and stored. Similarly, the estimation of geographic and socio-economic distribution of cases in the local community can be computed and proactively displayed.

INFLUENZA MODELING AND SIMULATION

A simulator for influenza outbreak scenarios must incorporate three types of models. The disease model represents the phases of the influenza infection. The population model represents the social structure of the local community. The intervention model represents the estimated effects of various interventions.

Representing influenza illness and transmission

Understanding and representing the mechanisms and speed with which influenza may be transmitted across human populations is crucial to effective pandemic preparation. Influenza can be transmitted through multiple mechanisms. Aerosolized droplets of respiratory secretions are the primary means of person-to-person influenza transmission, but spread can also occur through direct person-to-person contact or through contaminated objects (Bridges et al., 2003). The transmission speed in a population can be represented as a function of the reproductive number (R) and the serial interval, which is the average time between a primary and secondary case.

Figure 2 illustrates the phases of influenza infection in a susceptible person. A person infected by influenza first passes through a latency and incubation phase, after which he becomes infectious. During the infectious period, the infected person may or may not develop influenza symptoms. Persons with symptoms stop circulating and withdraw to their household with a given probability. Infected persons recover with immunity or succumb to the disease. The incubation period is 1–4 days with an average of 2 days (Cox & Subbarao, 1999). Persons can be infectious starting the day before symptom presentation through approximately 5 days after illness onset; children can be infectious for a longer period.

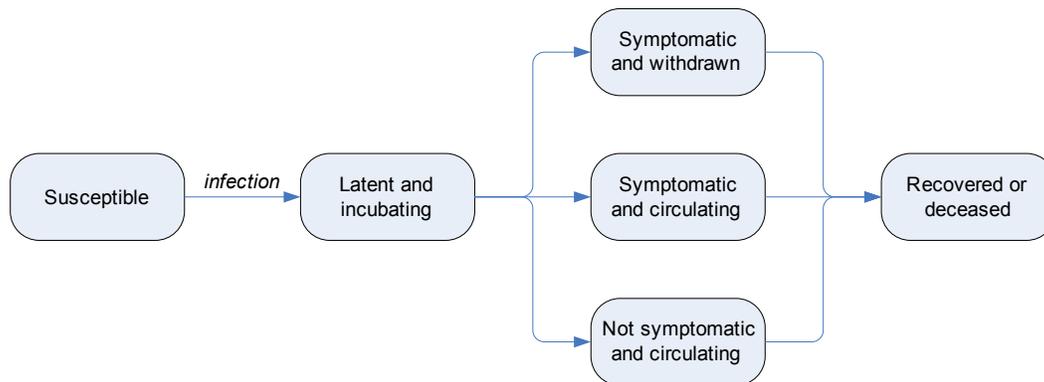


Figure 2: Influenza disease model

The basic reproductive number (R_0) is often calculated as a basis for analysis of different intervention strategies. It is defined as the average number of secondary infections produced by a randomly selected infected person in a fully susceptible population (Diekmann et al., 1990). For a heterogeneous population, it is the average of all the secondary cases that this randomly selected initial infective person would infect over all the social contexts of which she is a part. R_0 is often used as a threshold parameter that predicts whether an infection will spread (Heffernan et al., 2005). If $R_0 > 1$, the infectious agent is theoretically able to invade the susceptible population.

Modeling influenza outbreaks in local communities

Modeling influenza outbreaks requires the combination of a population model and a disease model. To support local decision makers, it is important that the combined model can represent disease outbreaks scenarios that capture specific local circumstances—for example, schools, workplaces, and mass transit hubs.

Stochastic, structured models have been used to study the transmission of influenza in populations of persons interacting in known mixing groups (Elveback et al., 1976; Longini et al., 2004; Longini et al., 2005; Timpka et al., 2005). A mixing group is a social context where people interact. Figure 3 illustrates some of the mixing groups in a population. Overlapping mixing groups, with defined contact rates and disease transmission probabilities, model the contacts a person makes during a specific period of time in various social contexts.

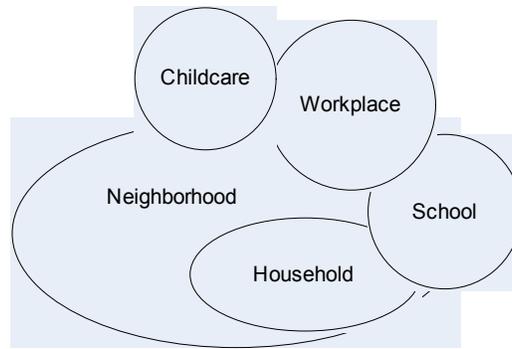


Figure 3: Sample mixing groups

Modeling interventions

Representing various interventions in a simulation of influenza outbreaks makes it possible to explore and evaluate alternative intervention strategies. Medical interventions reduce the transmission probability in contacts between infected and susceptible persons. Longini and his colleagues (2004) modeled influenza interventions with antiviral medication and vaccination. The antiviral drug decreases the probability that (1) a susceptible person becomes infected when exposed to infection, (2) that an infected person develops influenza symptoms, and (3) that an infected person transmits the disease to a susceptible person. Vaccination was modeled in the corresponding way. This type of interventions can be quantified as coefficients that modify the basic transmission probabilities assigned to mixing groups.

Interventions aimed at reducing the contact rates are represented as probabilities for individuals to withdraw from particular mixing groups. For example, shutting down schools eliminates interaction in the corresponding mixing groups, but may increase interaction in other groups, such as neighborhood and community.

SIMULATOR ARCHITECTURE AND IMPLEMENTATION

We present an architecture for simulating influenza outbreaks and describe its relationship to the decision-making workflow. Figure 4 summarizes the architecture (Eriksson et al., 2007). The main goal of separating modeling and model execution is to make it possible to use powerful tools to manage model complexity, while retaining computational efficiency.

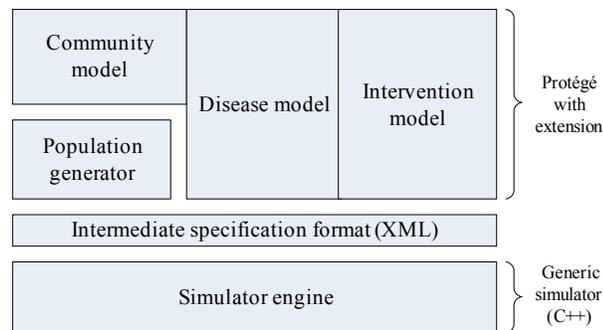


Figure 4: Architectural layers

Workflow

Planning and responding to pandemic influenza outbreaks require a collaborative effort. Simulation can support this process, but must be carefully integrated in the decision-making workflow. Figure 5 outlines a general workflow for intervention planning with a three-role planning committee consisting of a decision maker, an epidemiologist, and a scenario developer. The decision maker approves the intervention plan and is responsible for its implementation. The epidemiologist has the medical knowledge necessary to monitor the development of an outbreak and modifying

transmission and treatment parameters on the basis of emerging information and experience. The scenario developer's task is to design scenario models, to run the simulations, and to report the results.

An example of a typical loop in this workflow involves the following steps. In a planning session, the epidemiologist brings attention to the fact that a new effective anti-viral drug has become available, but at a limited supply and a high cost. The decision maker asks whether this drug should be considered in the intervention package, given budget and availability constraints. The scenario modeler prepares a number of scenarios, where assumptions

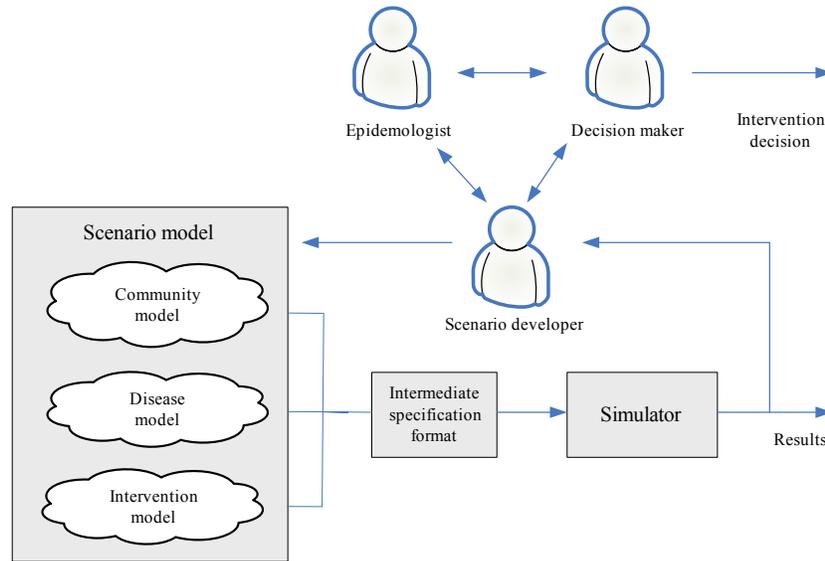


Figure 5: Workflow for decision support using scenario modeling and simulation

about the effectiveness of the drug, the number of doses available or affordable, and the target groups are combined to cover the scope of the question. Typically, the developer extends a basic model with scenario-specific concepts and instances. Because the scenario model is partitioned in community, disease, and intervention models, the scenario developer can modularize the work. In this case, a community model based on population data and geo-spatial information is assumed to already exist. Standard models for the most probable influenza strains are also expected to be available. Constructing a new instance from a template for anti-viral medication enables the scenario modeler to rapidly modifying the intervention model to include a representation of the new drug. Running the scenarios in the simulator generates estimates of the basic reproductive number that can be used to evaluate the cost and benefits of the new drug if included in the intervention package. In many cases, the planning team must use several iterations before they arrive at a conclusive answer.

In the response phase, new information about the properties of the disease and the effectiveness of various interventions may lead to modifications of the intervention strategy. Similarly, depleted or replenished resources can invalidate previous intervention strategies and thus necessitating a modification of the response plan. In any case, only the affected parts of the model need be updated.

Modeling environment

The modeling environment is based on the Protégé ontology-development environment, which provides several graphical tools for creating and editing ontologies (Gennari et al., 2003). Protégé manages the ontology with the community, disease, and intervention models. The Protégé-OWL editor is an extension of Protégé that supports the Web Ontology Language (OWL). OWL is one of the standard ontology languages, endorsed by the World Wide Web Consortium to promote the Semantic Web vision. An OWL ontology may include descriptions of classes, properties and their instances. The population generator in Figure 4, which is implemented as a Protégé extension in Java, expands the abstract community model to a set of generic mixing groups for use in the simulator engine. The intermediate specification format, which is XML-based, defines the mixing groups and their members as well as the disease and intervention model parts. The simulator engine then executes the simulation according to the specification. One of the advantages of the XML-based specification is that it makes it possible to transfer the

specification to alternative simulation-execution architecture, such as an array of machine performing parallel execution, such as performing repeated runs with different randomization in parallel.

Simulator engine

The simulator engine is based on a Longini-type simulator (Longini et al., 2004, Morin et al., 2005), which has been streamlined to only include functions for disease propagation, social mixing, and intervention implementation (Eriksson et al., 2007). An interface supports the communication of model specifications and simulation results between the modeling environment and the engine (see Figure 4). This separation of modeling and execution enables the design of a generic simulation engine and, thus, removes programming from the decision support workflow. The engine has been implemented in C++ for both Linux-based and Windows-based platforms. The simulator engine executes simulation jobs specified in the modeling environment. From the specification, it instantiates the virtual population, assigns initial cases of infection, and implement the prescribed intervention policy. For each time step of the simulation, the simulator engine propagates the state of infection in the population. First, the disease state of people in the incubating or infectious states is advanced. Recovering individuals acquire immunity. Then, each person susceptible to infection is exposed in her mixing groups. The simulation engine calculates the probability of becoming infected as the combined probability of becoming infected in any of the mixing groups. In each mixing group, that probability of becoming infected depends on the number of infected persons in that mixing group and the probability of transmission for each contact, which may be age dependent. The combined probability is used in a random binary test to determine whether the susceptible person becomes infected. Persons that become infected transition to the incubating state. As an example, a child who attends elementary school participates in four mixing groups: household, school, neighborhood, and community. In those mixing groups, she is exposed to the number of child and adult infectious persons in her household, I_{hc} and I_{ha} ; in her school, I_s ; in her neighborhood, I_n ; and in the population, I_c , with corresponding transmission probabilities for each contact of p_{hcc} (child to child), p_{hac} (adult to child), p_s , p_n , and p_c , respectively. The probability P that the child becomes infected that day is

$$P=1-(1-p_{hcc})^{I_{hc}}(1-p_{hac})^{I_{ha}}(1-p_s)^{I_s}(1-p_n)^{I_n}(1-p_c)^{I_c}$$

A uniform [0, 1] random number is selected. If the number is less than P , the child becomes infected and enters the incubating state.

SIMULATION EXPERIMENTS

In our simulation experiments, we used a spatially explicit, geo-physical model of a virtual city based on Linköping, Sweden (Figure 6). The scenario included mixing groups for households, neighborhoods, schools, daycare centers, and play groups. Children were assumed to attend local elementary and middle schools ($n=45$), whereas adolescents are randomly assigned to city high schools ($n=5$).

To measure the effectiveness of interventions, we estimated R_0 under various intervention strategies. We randomly selected and infected a person from the fully susceptible population ($n=135,800$) and counted the number of secondary cases infected by that person. The average number of secondary cases from 1,000 such samples represented R_0 . We took as the resulting estimate of R_0 the mean over 100 populations generated from the same population data.

Persons infected by influenza are assumed to pass through two phases (c.f. Figure 2). The first phase is an incubation period when they are not infectious. The second phase is the infectious period. The lengths of the incubation and infectious periods follow empirical probability distributions, with mean lengths of 1.9 and 4.1 days, respectively (Anderson & May, 1991; Brookmeyer, 2004). During the infectious period, the infected person may or may not develop influenza symptoms. The probability that a person will be symptomatic given that person has been infected is 0.67. An asymptomatic infection is assumed to be 50 percent as infectious as a symptomatic infection. In

Virtual city school structure		Population age distribution		Household type (%)	
Pupils	36,800	Children, 0–6	8,800	1 person	41
Day care centers	140	Children, 7–18	28,000	2 persons	32
Elementary schools	65	Adults, 19–65	85,000	3 persons	10

Middle schools	26	Elderly, 66–	14,000	4 persons	12
High schools	5	Total	135,800	5 persons	4
				Other	1

Figure 6: Virtual City population model data sheet

the model, the probability that persons with symptoms withdraw to the household is 0.67, exposing only the other members of their household. People who do not withdraw continue circulating in their mixing groups.

In our scenarios, we examined two intervention types: medical and physical. The medical intervention scenarios used two different vaccines with good and poor effect on the specific influenza strain. We also varied the number of vaccine doses available. Vaccination decreases the probability that a susceptible person becomes infected when exposed to infection and that an infected person transmits the disease to a susceptible person. These effects were quantified and represented as coefficients, M_{sus} and M_{inf} , respectively, which were multiplied to the transmission probabilities assigned to mixing groups. The good vaccine had $M_{sus} = 0.3$ and $M_{inf} = 0.2$ and the poor vaccine had $M_{sus} = 0.6$ and $M_{inf} = 0.35$. In the physical intervention scenarios, a selection of schools and daycare centers were closed, thus eliminating interaction in the corresponding mixing groups. We developed three scenarios involving physical interventions: daycare centers closed, high schools closed, and all schools and daycare centers closed.

Mixing group	Transmission probability among children
Playgroup	0.04
Daycare center	0.015
Elementary school	0.0145
Middle school	0.0125
High school	0.0105

Table 1. Basic transmission probabilities in schools and playgroups

Mixing group	Preschool children	School children	Adults
Household	0.08	0.08	0.04
Neighborhood	0.00004	0.00012	0.00016
Community	0.00001	0.00003	0.00004

Table 2. Basic transmission probabilities in the household and neighborhood mixing groups

Tables 1 and 2 give the basic transmission probabilities in the various mixing groups. Without interventions, the probabilities in Tables 1 and 2 applied. However, in the presence of interventions, these probabilities were reduced according to the intervention model. Table 3 lists the results of the simulation experiments. For each scenario the estimated R_0 is stated together with its standard deviation. For comparison, ΔR_0 gives the difference to the case with no interventions.

Intervention	R_0	<i>S.D.</i>	ΔR_0
No interventions	2.23	0.24	0
Daycare centers closed	2.20	0.21	-0.03
High schools closed	1.32	0.094	-0.91
All schools closed	0.53	0.025	-1.70
Well matched vaccine: 5,000 doses	1.90	0.18	-0.33

Well matched vaccine: 15,000 doses	1.42	0.15	-0.81
Poorly matched vaccine: 5,000 doses	1.95	0.19	-0.28
Poorly matched vaccine: 15,000 doses	1.51	0.16	-0.72

Table 3. R_0 for different interventions in the virtual city

DISCUSSION

We have presented a simulation architecture and its relation to the decision-making workflow at local agencies preparing and responding to outbreaks of pandemic influenza. A crucial insight underlying this research is that intervention planning is always performed with incomplete and uncertain information; hence the iterative approach. Separating modeling from simulation allows the use of specialized tools, such as the Protégé ontology-development environment for modeling, and an optimized simulator for simulating the models. As soon as there is a need to modify the models and handle multiple versions, this approach will save implementation time and, in particular, testing effort. Other benefits of the Protégé environment are the support for model reuse, based on the concept classes, and the possibility to extend the user interface. One apparent extension is to provide tools for presenting and analyzing simulation results. The models can be further refined to capture additional social contexts. Workplaces have been modeled in other simulations (Germann et al., 2006) and are a natural extension to our present representations. Introducing a difference between workdays and holidays makes it possible to more accurately represent community life over time. On workdays, children go to school and adults work; on holidays people spend time with friends and family in neighborhoods and households. Model validation is an important issue to consider when interpreting simulation results, but it is also generally acknowledged as a difficult problem (e.g., Elveback et al., 1976; Longini et al., 2004), mainly due to the fact that the specific transmission properties of a pandemic influenza strain cannot be fully known in advance. We do not claim that our simulation results are correct in terms of absolute numbers. However, we argue that relative results are interesting, because they make it possible to compare the effectiveness of different interventions in a particular virtual community based on actual population data. Significant differences in R_0 indicate differences in intervention effectiveness. The primary source of knowledge regarding transmission probabilities is the research literature on influenza. However, the probabilities arrived at in the studies apply to particular outbreaks and communities under specific conditions. Generalizing them is not a straightforward task. Validation using historical illness data is one way of increasing confidence. A more valid approach would be to tune models using actual feedback data from bio-surveillance systems. Such surveillance systems have today been implemented as countermeasures against bio-terrorism (Lewis et al., 2002). Simulator execution time is a critical factor in the decision-making workflow. In the present implementation, the simulation of one scenario takes approximately five hours on a high-performance PC for a population of 140,000 people. This delay may be acceptable in the planning phase, where several scenarios can be prepared and run as a batch job. In the response phase, however, it is probably unacceptable. One advantage of the simulation architecture is that it includes an intermediate specification format (c.f. Figure 4). This format makes it possible to partition the job of running a scenario to multiple simulators. In our continuing research, we intend to develop this feature to target both a PC cluster super computer and an office network of workstations and servers at Linköping University. Being able to use standard office computers for running simulations in parallel opens up the possibility to shorten the time required to complete a scenario considerably.

CONCLUSION

Simulation is a valuable tool for local-level decision support before and during outbreaks of pandemic influenza. However, incomplete, uncertain, and dynamic information necessitates an iterative approach to decision making in preparedness and response. Correspondingly, a simulation architecture must support an iterative workflow in a collaborative setting. The method of formulating scenarios and comparing the simulation results of these scenarios allows decision makers in local communities and regions to custom-tailor interventions for specific population and resource conditions. Furthermore, it is useful to divide the scenario model in subparts for communities, diseases, and interventions and to support construction of new scenarios from these components. Protégé, combined with the scenario extension, provides a modeling environment that uses ontologies to define the scenarios and scenario modules. The successful separation of modeling in Protégé from execution of simulation jobs in the generic simulation engine is an important step towards bringing the simulations closer to the decision maker in a pandemic influenza situation.

ACKNOWLEDGMENTS

This work was supported in part by the Swedish Emergency Management Agency (KBM) under contract 0700/2004 and in part by the Swedish Research Council under contract 2006-4433.

REFERENCES

1. Anderson, R. M. & May, R. M. (1991). *Infectious Diseases of Humans: Dynamics and Control*. Oxford: Oxford University Press.
2. Brehmer, B. (1992). Dynamic decision making: Human control of complex systems. *Acta Psychologica*, 81, 211–241.
3. Bridges, C. B., Kuehnert, M. J. & Hall, C. B. (2003). Transmission of influenza: implications for control in health care settings. *Clinical Infectious Disease*, 37, 1094–1101.
4. Brookmeyer, R. (2004). Temporal factors in epidemics: the role of the incubation period. In: Brookmeyer, R. & Stroup, D. F. (eds.), *Monitoring the health of populations*. Oxford: Oxford University Press, 127–146.
5. Cox, N. J. & Subbarao, K. (1999). Influenza, *Lancet*, 354, 1277–1282.
6. Diekmann, O., Heesterbeek, J. A. P. & Metz, J. A. J. (1990). On the definition and the computation of the basic reproductive ratio R_0 in models for infectious diseases in heterogeneous populations. *Bulletin of Mathematical Biology*, 28, 365–382.
7. Elveback, L. R., Fox, J. P. & Ackerman, E., Langworthy, A., Boyd, M. & Gatewood, L. (1976). An influenza simulation model for immunization studies. *American Journal of Epidemiology*, 103, 152–165.
8. Eriksson, H., Morin, M., Jenvald, J., Gursky, E., Holm, E., & Timpka, T. (2007). Ontology Based Modeling of Pandemic Simulation Scenarios. In *Proceedings of the Medinfo triennial congress*, Brisbane Australia, August 20–24.
9. Ferguson, N. M., Cummings, D. A., Fraser, C., Cajka, J. C., Cooley, P. C. & Burke, D. S. (2006). Strategies for mitigating an influenza pandemic. *Nature*, 442(7101), 448–452.
10. Gennari, J. H., Musen, M. A., Ferguson, R. W., Grosso, W. E., Crubézy, M., Eriksson, H., Noy, N. F. & Tu, S.W. (2003). The evolution of Protégé: An environment for knowledge-based systems development. *International Journal of Human Computer Studies*, 58(1), 89–123.
11. Germann, T. C., Kadau, K., Longini I. M. & Macken C. A. (2006). Mitigation strategies for pandemic influenza in the United States. *Proceedings of the National Academy of Science of the United States of America*, 103(15), 5935–5940.
12. Heffernan, J. M., Smith, R. J. & Wahl, L. M. (2005). Perspectives on the basic reproductive ratio. *Journal of the Royal Society Interface*, 2(4), 281–293.
13. Lewis, M. D., Pavlin, J. A. Mansfield, J. L. O'Brien, S. Boomsma, L. G. Elbert, Y. & Kelley P. W. (2002). Disease outbreak detection system using syndromic data in the greater Washington DC area, *American Journal of Preventive Medicine*, 23(3), 180–186.
14. Longini, I. M., Halloran, M. E., Nizam, A. & Yang, Y. (2004). Containing pandemic influenza with antiviral agents, *American Journal of Epidemiology*, 159, 623–633.
15. Longini, I. M., Nizam, A. & Xu, S., Ungchusak, K., Hanshaoworakul, W., Cummings, D. A. T. & Halloran, E. M. (2005). Containing pandemic influenza at the source. *Science*, 309, 1083–1087.
16. Meade, M. S. & Earickson, E. J. (2005). *Medical geography* (2ed.). New York: The Guildford Press.
17. Morin, M., Eriksson, H., Jenvald, J., & Timpka, T. (2005) Simulating influenza outbreaks in local communities. In *Fritzon P, ed. Proceedings of Biomedical Simulation Conference 2005*. Amsterdam: IOS Press, 2005.
18. Timpka, T., Morin, M., Jenvald, J., Eriksson H., & Gursky E. A. (2005). Towards a simulation environment for modeling of local influenza outbreaks. In *Proceedings of the AMIA Annual Symposium*, Washington, D.C., October 22–26.
19. Timpka, T., Morin, M., Jenvald, J., Gursky E., & Eriksson, H. (2007). Dealing with ecological fallacy in preparations for influenza pandemics: Use of a flexible environment for adaptation of simulations to household structures in local contexts. In *Proceedings of the Medinfo triennial congress*, Brisbane Australia, August 20–24.