EpiSimS Simulation of a Multi-Component Strategy for Pandemic Influenza

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Abstract

Limited stockpiles of antiviral medications and lack of availability of early strain-specific vaccine will require a multi-component strategy of pharmaceutical and non-pharmaceutical measures to delay or contain a future catastrophic avian influenza pandemic. A strategy composed of the antiviral stockpile distribution, school closures, and social distancing, followed by strain-specific vaccine when available is proposed. The EpiSimS agent-based simulation model with a structured population is used to assess the effectiveness of this strategy and to explore the sensitivity of its elements, in particular the level of school closures and the start time for non-pharmaceutical interventions, with varying amounts of expected fear-based isolation behavior. Results show that the level of school closure has the largest effect on reducing morbidity and mortality, comparable to US seasonal flu when starting early with a high level of school closures. Small variations of fear-based isolation showed little impact on morbidity and mortality, though a large second-order effect is seen on worker absenteeism.

1. INTRODUCTION

The H5N1 strain of avian influenza continues to be a global public threat, making it a likely source for a future pandemic [Holmes 2005, Juckett 2006]. The rapid spread of influenza, its short incubation period, limited antiviral medication supplies [U. S. Department of Health and Human Services 2006], lack of early effective vaccines [Fedson 2003], and increased air travel pose a significant challenge to the design of useful intervention strategies for such an event. Combinations of pharmaceutical interventions such as distribution of antiviral medication and vaccine coupled with non-pharmaceutical interventions (school or workplace closures, household quarantine, social distancing, travel restrictions) may prove to be the best defense, since their potential to delay or contain an influenza pandemic has been shown [Ferguson 2005, Germann 2006, Glass 2007].

Our first defense against pandemic flu is the ability to see it coming. Ongoing surveillance is required to detect and track increases in influenza-like illness (ILI) [U. S. Department of Health and Human Services 2005, 2007] especially for new strains such as H5N1. The national influenza surveillance system will provide the virologic and disease surveillance data needed to guide response efforts during a pandemic [CDC 2007]. Case counts are based on weekly data of reported outpatient visits for ILI, hospitalizations, and deaths. These are not exact. These are the best estimates available to decision-makers to determine when to start intervention control measures.

Antivirals could be important in the early stages of a pandemic influenza in the absence of a strain-specific vaccine [Hayden 2001, Longini 2004, Gani 2005, Monto 2006]. Currently, the federal government has only stockpiled enough antiviral courses for approximately 6.7% of the population [U. S. Department of Health and Human Services 2006]. This is insufficient to provide adequate long-term prophylaxis for the entire population, or even for high-risk populations. Similarly, strain-specific vaccine may not be available till the later stages of a pandemic. Current production of seasonal influenza vaccine in the United States is assumed to be 3-5 million doses per week with 3-8 months required for development [U. S. Department of Health and Human Services 2005, U. S. Government Accountability Office 2004]. This will be similar for a pandemic influenza strain-specific vaccine, with two doses per person required due to the absence of pre-existing immunity [World Health Organization 2006]. Non-pharmaceutical interventions will be required until adequate supplies of vaccine and antivirals are available [World Health Organization Writing Group 2006].

Interventions targeting children such as school closures could prove beneficial since children play a major role in the spread of influenza due to their extra-household contacts with peers in school or daycare, increased susceptibility, and increased viral shedding [Viboud 2004]. This contributes to the burden on the healthcare system, results in increased worker absenteeism for parents staying home with sick children, and causes secondary illnesses among household members [Tsolia 2006, Carrat 2002, Neuzil 2002]. Schools were closed during the SARS outbreak, which helped control its spread [Pang 2003]. Another example was observed during the 1959 pandemic, in which attack rates decreased during summer school closures [World Health Organization Writing Group 2006]. Currently, school closures continue to show a dramatic decline in seasonal influenza morbidity [Heymann 2004]. The CDC has recommended closing schools from one to three months if the next pandemic is similar to the 1918 influenza pandemic [CNN 2007a].

People will modify their behavior to prevent themselves from getting infected or be encouraged through the public health system. The news of increasing numbers of people becoming ill, or seeing friends and family fall ill, are strong motivations to avoid potential disease spreading situations causing some people to isolate to their homes out of fear as a reaction to an epidemic crisis. Social distancing measures become useful when one cannot stay home by choice or due to the fact that 47% of the nation's private sector workforce has no paid sick leave [CNN 2007b]. These include maintaining a minimal three-foot distance from colleagues, refraining from handshakes and other familiar greetings, frequent hand washing, cough etiquette and respiratory hygiene, and use of masks.

It is important to assess the impact that non-pharmaceutical interventions could have on future disease spread and how they can be optimized [Del Valle 2005]. A number of studies have evaluated the impact of behavioral changes such as school closures, social distancing, and travel restrictions, under different scenarios for pandemic influenza [Ferguson 2005, Germann 2006, Colizza 2007], with most assuming that these behavioral modifications would remain in effect for the duration of the pandemic, though lack of resources may limit compliance.

This study assesses the impact of a multi-component intervention strategy of administration of the 6.7% stockpile of antivirals to sick individuals and their household members coupled with school closures and social distancing, followed by distribution of a strain-specific vaccine when it becomes available. Sensitivity to the level of school closures, start time for the non-pharmaceutical measures, and amount of expected fear-based isolation behavior is explored.

2. METHODS

The epidemic simulation engine, EpiSimS [Stroud 2007], was used to model the spread of influenza in six counties in southern California, consisting of Los Angeles, Orange, Riverside, San Bernardino, San Diego, and Ventura counties. EpiSimS is a C++ application that runs on high-performance computing clusters. It is a stochastic agent-based discrete event model that explicitly represents every person in a city, and every place within the city where people interact. A city or region is represented physically by a set of road segment locations and a set of business locations. The synthetic population was constructed to statistically match the 2000 population demographics of southern California at the census tract level, consisting of 18.8 million individuals living in 6.3 million households, with an additional 938,000 locations representing actual schools, businesses, shops, or restaurant addresses. Each person as an agent in the simulation is assigned a schedule of activities to be undertaken throughout the day. There are eight types of activities: *home*, *work*, *shopping*, *visiting*, *social recreation*, *passenger server*, *school*, and *college*; plus a ninth activity designated *other*. Information about the time, duration, and location of activities is obtained from the National Household Transportation Survey [U. S. Department of Transportation 2003]. The integration of the population, activities, and geo-referenced locations forms the dynamic social network in EpiSimS.

The number of people at a location at any time varies widely, from zero up to many thousands. Not every pair of individuals who happen to be at the same location at the same time will be close enough to transmit disease. In EpiSimS, each location is partitioned into one or more *rooms* or *mixing groups* where the various types of activities take place. Disease transmission events can only occur between individuals that occupy the same room at the same time. A school activity at a *location* will be sub-divided into *classrooms*, while work activities will be split into *workrooms* with sizes set according to standard industry classification (SIC) codes. All households on a city block are represented as a single geo-referenced *location*, which is divided into separate *rooms*, each representing an individual home.

The epidemiology of the future influenza virus is not known and it will not be known until it emerges, therefore, our influenza disease model is based on historical data and previous epidemic models. Disease progression in EpiSimS is characterized by 14 states [Stroud 2007]. A susceptible individual after becoming infected progresses through a sequence of disease states, beginning with non-infectious incubation followed by a pre-symptomatic infectious stage. From there, an individual can become symptomatic-infectious, or asymptomatic-infectious. The asymptomatic-infectious individuals pass through a less-infectious stage and then recover. The symptomatic-infectious individuals either are not sick enough to curtail their activities or so sick that they must stay home (non-circulating). Those that continue their activities pass through a less-infectious stage and then recover. Those symptomatics that stay home split into manifestations with and without severe complications such as pneumonia that would require hospitalization. Non-circulating symptomatics will either die or progress through a convalescent stage on their way to recovery. The duration of each state is a stochastic variable, with distributions of sojourn times matched to case history distributions (Longini 2004).

Scenarios are constructed as a set of parameterized specifications of behavior modifications, pharmaceutical interventions, and/or non-pharmaceutical interventions sequenced by start and stop times, with some overlapping. Descriptions of the scenario elements used in the multi-component strategy follow.

In every scenario, people self-isolate to their homes while they are incapacitated. A household adult will stay home with a sick child and abstain from their non-home daily activities until the child has recovered.

In EpiSimS, ten-day courses of antivirals are delivered to sick individuals for therapeutic treatment and as prophylactic treatment to their household members starting on the first day. This reduces the probability of transmission by a factor of 5 only during treatment. It is assumed that 95% of household contacts will accept treatment. Those who receive prophylaxis and are exposed during treatment have a 20% chance of becoming infected. In the scenarios, it is assumed that there are only enough antiviral courses available for 6.7% of the population based on the U. S. stockpile in the simulations.

School closures in EpiSimS are implemented as a general closure of selected activity locations. Based on the CDC pandemic guidelines [CNN 2007a], closures follow a step-like function and are specified in EpiSimS with a start and stop time, the activity to close, and the location. The location can be specified as a single location or a fraction of all locations of the specified activity type that will be closed. During the time a closure is in effect, anyone whose activity schedule would have taken them to one of the closed locations will go home during that time instead. They will follow their other scheduled activities as usual. At least one household adult will stay home with a child who is isolating due to a school closure. Given the fraction of schools to be closed, schools are chosen at random from the six counties in southern California. In the scenarios, 20% and 100% of schools are closed for 5 months.

Fear-based home isolation is used to simulate people staying home as a reaction to an epidemic crisis. Some of these people may be considered the "worried well." It is assumed that people isolate due to fear at a level that follows the pattern of the epidemic. That is, fear-based home isolation is modeled by a triangle function, specified with start, peak, and end times and corresponding fractions of the population that will be isolating at those times, along with a minimum and maximum contiguous duration per individual. Since it may not be feasible for many people to stay home for long periods of time (due to lack of resources), it is assumed that people who choose to stay home will only self-isolate for 7 to 14 days. In the simulation, when fear-based home isolation is in effect, at the beginning of each simulated day the percentage of the population that should be isolating that day is calculated and if required, people are added randomly from those not currently isolating. When a person goes into fear-based home isolation, a contiguous duration of 7-14 days is chosen from a uniform distribution. Once people go out of fear-based home isolation, others start and they are also eligible to go back to fear-based home isolation for another duration. This behavior is implemented synchronously in the 3978 census tracts of southern California. People isolate on an individual basis, not on a household basis, so there might be households in which some members of the family are isolating due to fear and others are going about their daily activities. In the scenarios, fear-based isolation continues for 5 months with peaks of 5%, 10%, and 15% of the population.

Social distancing is implemented in the EpiSimS model as a reduction in the probability of infection. Children age six and under do not participate. It is assumed that social distancing reduces both the susceptibility and infectiousness of the population by a certain percentage during their non-household related interactions. These behavioral modifications are specified with a start and stop time. In this strategy, 10% social distancing with 85% compliance is in effect across all non-home activities as part of all multi-component scenarios.

Based on the typical seasonal influenza vaccine production, an estimate of 4 million doses per week was used with vaccine becoming available after 5 months. It is assumed that a limited number of courses, enough to cover 0.67% of the population of southern California per week will become available five months after the emergence of pandemic influenza. Vaccine is distributed to households at random in EpiSimS until supplies run out, with 95% of selected household members being vaccinated. The vaccine approach used in this study is a per person course of two doses of pandemic vaccine taken 1 month apart providing an immune response of near 80% seropositivity after 42 days from the first dose [Lin 2006]. Complete immunity is assumed in 80% of the recipients. If any of the 20% of vaccinated persons that do not develop immunity become infected, they would be only one fifth as infectious as their unvaccinated counterparts. Every unvaccinated household has an equal chance of receiving the next available course.

Each simulation scenario yields tabulations of epidemic parameters, new infections per activity, and worker absenteeism statistics. The epidemic parameters include daily counts of new infections, symptomatics, mortality, etc. overall and by demographic group (ex. preschool, youth, adult, senior). Daily activity counts show the numbers of individuals that became infected during activities such as home, work, shopping, visiting, social recreation, passenger server, school, college, and other. Daily fractions of the working population that are absent due to illness, death, or other (ex. staying home with children due to illness or school closure or fear) are assembled, along with the cumulative days lost.

3. RESULTS

The homeland security council suggests that the emergence of a new influenza virus could have a clinical disease attack rate of 30% in the overall population [U. S. Homeland Security Council 2006]. Scientists have determined that pandemic flu strains tend to infect between 25% and 35% of the population based on evidence from the three pandemics that occurred during the 20th century. A baseline scenario was constructed under the assumption of no specific intervention to contain the pandemic and an infection attack rate of 45% with a clinical attack rate of 30%. A value for the reproductive number $\Re_0$ of 1.8 was calculated for the baseline, which is in agreement with estimated reproduction numbers for pandemic influenza [Longini 2004, Ferguson 2005]. People are assumed to self-isolate to their homes while they are incapacitated in all scenarios.

3.1. Epidemic

Our simulations show that a multi-component strategy provides an effective way to reduce the spread of the epidemic. A stockpile of antiviral courses for 6.7% of the population is available from the beginning of the simulation. Non-pharmaceutical interventions of school closure, and social distancing, along with fear-based isolation behavior are started when different percentages of the population are symptomatic lasting for 5 months, overlapping vaccine delivery. A 2-dose, 80% effective vaccine becomes available at 5 months. A suite of scenarios was run varying school closure level, non-pharmaceutical intervention start, and peak population isolating due to fear. A low level of 20% school closures was considered, as well as a high level of 100%. For each level of school closures, interventions started when 0.01%, 0.1%, and 1.0% of the population is symptomatic (day 30, 53, and 80). For each level of school closures and interventions beginning only when 0.1% of the population is symptomatic, peak fear isolation was varied between 5%, 10%, and 15%. 10% social distancing is used in all cases.

Table 1 shows that in the absence of any intervention, the model predicts a 30.6% clinical attack rate and 614 influenza related deaths per 100,000 persons in the population. The results are ordered by clinical attack rate (the percentage of the population that was ever symptomatic) in Table 1. All tables in this report use the same ordering for easy comparison. The level of school closure has the largest effect. 20% school closures reduce the clinical attack rate by 5-10%. 138-239 more lives are saved per 100,000. Interventions starting at 1.00% with a 100% school closure are similar to the lower level of school closure. The rest of the 100% school closure results show low morbidity and mortality, less than that for US seasonal flu. Starting interventions when 0.01% of the population is symptomatic with a low level of school closures provides the least improvement since the 5 months of interventions are let up before the pandemic has been contained. Starting interventions when 0.01% of the population is symptomatic provides the best results with a high level of school closures, but a 0.10% start may be more realistic and provides similarly good results (note shaded lines in Table 1).

Table 1. Epidemic results for different variations of a multi-component intervention strategy.

% of Population Symptomatic at Start of Interventions	% School Closure	% Peak Fear Isolation	Clinical Attack Rate %	Mortality per 100,000
Baseline	-	-	30.6	614
0.01	20	15	25.5	476
1.00	20	15	22.7	421
0.10	20	5	22.1	410
0.10	20	10	20.6	381
0.10	20	15	20.4	375
1.00	100	15	18.6	335
0.10	100	5	0.6	4
0.10	100	10	0.5	4
0.10	100	15	0.3	2
0.01	100	15	0.1	0.4

The entire 6.7% stockpile of antiviral medications is distributed whether starting interventions when 1.00% of the population is symptomatic or with a low level of school closures. The 2-dose, 80% effective vaccine is distributed to over one fourth of the population in these cases. Vaccination of a smaller portion of the population indicates a shorter pandemic, either due to being uncontained with a low level of school closures or being contained quickly with a high level of school closures.

In Figure 1A-D the symptomatic percentage of the population as a function of time is shown for the baseline and multi-component strategy variants with 20% school closures and starting interventions when 0.01%, 0.10%, and 1.00% of the population is symptomatic (days 30, 53, and 80). The 20% school closure, 10% social distancing, and 15% fear-based isolation are relaxed after 5 months due to the availability of a strain-specific vaccine. Starting interventions at 0.01% is too early since the pandemic is only partially contained within 6 months. Starting interventions at 1.00% appears to be a little late, but does reduce the symptomatic peak to about 5.5% compared to about 10% for baseline. Starting at 0.10% provides the best containment for this situation, though given the slow delivery rate of vaccine courses, a small second wave of cases appears. The multi-component strategy with a low level of school closures provides a low level of containment and is able to delay the spread of a pandemic.

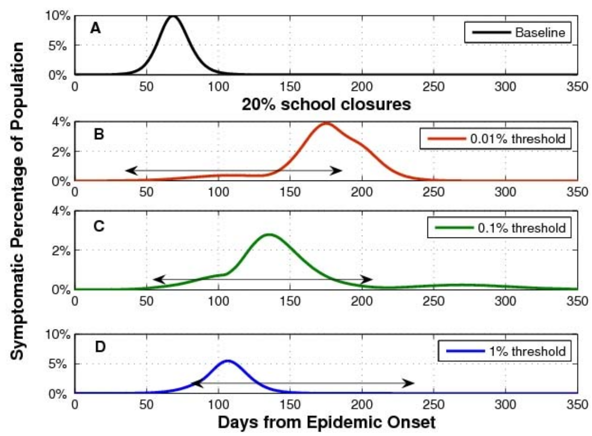

Figure 1. Symptomatic percentage of the population as a function of time for the baseline and multi-component strategy with 20% school closures and varying non-pharmaceutical intervention start time: (A) baseline, (B) 0.01%, (C) 0.1%, and (D) 1.0%.

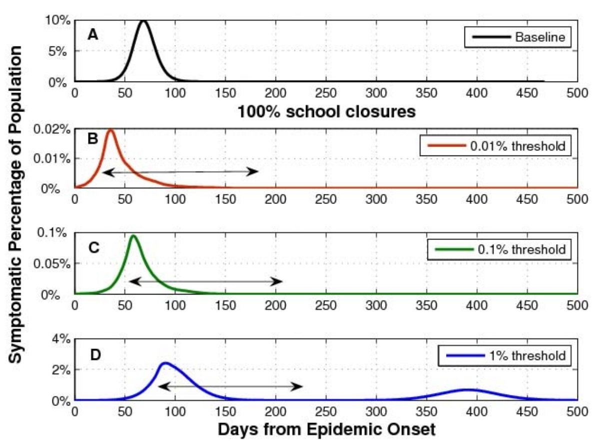

Figure 2. Symptomatic percentage of the population as a function of time for the baseline and multi-component strategy with 100% school closures and varying non-pharmaceutical intervention start time: (A) baseline, (B) 0.01%, (C) 0.1%, and (D) 1.0%.

In Figure 2A-D the symptomatic percentage of the population as a function of time is shown for the baseline and multi-component strategy variants with 100% school closures and starting interventions when 0.01%, 0.10%, and 1.00% of the population is symptomatic (days 30, 53, and 80). The 100% school closure, 10% social distancing, and 15% fear-based isolation are relaxed after 5 months due to the availability of a strain-specific vaccine. Starting interventions at 0.01% and 0.10% allows the pandemic to be contained before much vaccine is available. Starting interventions at 1.00% contains the epidemic effectively until vaccine is available, but given the slow delivery rate of vaccine courses, a small second wave of cases appears. A multi-component strategy with a high level of school closures provides a high level of containment. The sooner it is started, the better the results are.

Varying the peak percentage of fear-based isolation behavior between 5%, 10%, and 15% with a low level of school closures and starting interventions when 0.10% of the population is symptomatic does not cause a significant difference in morbidity and mortality, as seen in Table 1, though the symptomatic peak % decreases with more fear-based isolation, as seen in Figure 3A-D. There is a similar effect with a high level of school closures.

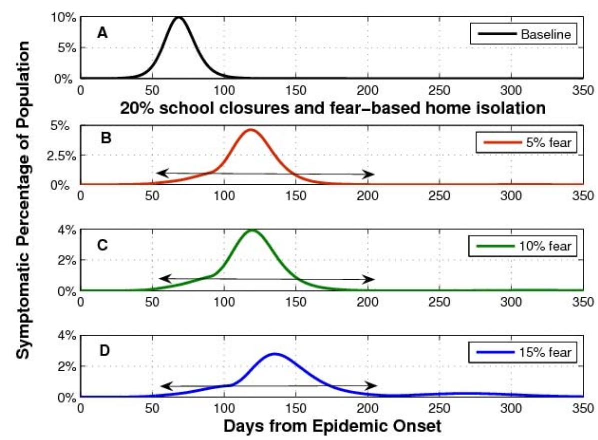

Figure 3. Symptomatic percentage of the population as a function of time for the baseline and multi-component strategy with 20% school closures and varying the peak percentage of people isolating due to fear: (A) baseline, (B) 5%, (C) 10%, and (D) 15%.

3.2. Worker Absenteeism

Table 2 shows the peak percentage of worker absenteeism and cumulative days absent per worker for the multi-component strategy. Level of school closures is not correlated with worker absenteeism, since workers staying home with children contribute only a small fraction. In the multi-component strategy, more fearful people result in more worker absenteeism. High peak absenteeism of about 18% results from a 15% peak fear isolation behavior, while around half that for 5% peak fear. Low levels of fear contribute to less lost days (note shaded lines in Table 2.).

Table 2. Results for peak worker absenteeism and cumulative absent days per worker.

			Worker Absenteeism	
% of Population Symptomatic at Start of Interventions	% School Closure	% Peak Fear Isolation	Peak %	Cum Days
baseline	-	-	7.97	2.79
0.01	20	15	16.81	15.37
1.00	20	15	17.05	14.68
0.10	20	5	9.32	7.86
0.10	20	10	14.07	11.66
0.10	20	15	18.25	15.32
1.00	100	15	18.06	17.65
0.10	100	5	7.91	8.07
0.10	100	10	12.88	10.79
0.10	100	15	17.76	15.08
0.01	100	15	17.71	14.11

4. DISCUSSION

A multi-component strategy for pandemic influenza composed of distribution of the currently available national stockpile of antivirals for therapeutic and prophylactic treatment coupled with school closures and social distancing along with expected fear-based isolation behavior could potentially delay or contain the spread of a pandemic until a strain-specific vaccine becomes available. An agent-based simulation model with a structured population was used to demonstrate this. The sensitivity to level of school closures, start time of the non-pharmaceutical interventions, and amount of fear were assessed in this work.

The level of school closures has the largest effect. Simulations show that a low level of school closures provides limited reductions in morbidity and mortality, though still lower than baseline. The entire 6.7% antiviral stockpile and enough vaccine for about 25% of the population are necessary in this case, due to a lengthened pandemic. A high level of school closures when non-pharmaceutical interventions are started early is required to produce significant reductions in morbidity and mortality, less than US seasonal flu. Starting later may require more than the 5 months of non-pharmaceutical interventions to prevent a second wave due to the slow rate of vaccine delivery. Less than the antiviral stockpile and a small portion of available vaccines are used when school closures are at a high level due to a shortening of the pandemic.

The accuracy of when non-pharmaceutical interventions are started is dependent on high-quality surveillance. Starting when 0.1% of the population is symptomatic, provides the best compromise for low and high levels of school closures. Interestingly, with a low level of school closures, the pandemic is delayed longer when starting earlier, while the opposite effect is seen with a high level of school closures.

In reality, fear in the population cannot be controlled. Small differences in the amount of fear-based isolation behavior, peaking at 5-15%, with all other elements kept constant, showed little impact on morbidity and mortality, though a large second-order effect is seen on worker absenteeism. The economy can be adversely affected by workers staying home due to fear, resulting in more lost worker-days. Adult workers that stay home with children who are sick or at home due to school closure additionally contribute a small amount to worker absenteeism.

This multi-component strategy of pharmaceutical and non-pharmaceutical interventions was shown to be effective, especially with an early start and a high level of school closures. Simulations show that the suggested non-pharmaceutical interventions are able to contain a pandemic until vaccine is available, even with the current low vaccine production rate. Advances in vaccine development enabling earlier availability and increased production rates such as a cell-based approach could lessen the time of non-pharmaceutical interventions.

The EpiSimS agent-based simulation model is a useful tool for understanding the sensitivity of elements in an intervention strategy such as proposed in this work, the potential results, and implications.

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Biography

Susan Mniszewski is a Technical Staff Member in the Information Science Group at Los Alamos National Laboratory. Her current work includes the design and development of parallel high performance computing software for the EpiSimS agent-based discrete event disease simulation tool, as well as modeling of pandemic influenza intervention scenarios. She also contributes to projects such as parallel hydrological modeling, service-oriented architectures for simulation environments, and protein function prediction. She is a member of IEEE Computer Society and ACM.

Sara Del Valle completed her Ph.D. in Applied Mathematics and Computational Sciences at the University of Iowa in May 2005, where she worked on analyzing the effects of behavioral changes and mixing patterns in mathematical models for smallpox epidemics. During graduate school she received an Alfred P. Sloan Fellowship and she worked at the Center for Nonlinear Studies (CNLS) under the supervision of the 2003 Ulam scholar. After earning her Ph.D. she joined Los Alamos National Laboratory as a postdoc in CCS-5 (Discrete Simulation Science Group). After only 8 months as a postdoc, she was converted to Technical Staff Member in D-3 (Systems Engineering and Integration Group). Sara has worked on developing and analyzing mathematical models for the spread of infectious diseases and she is part of the Epidemic Simulation System (EpiSimS) team and BioWatch team. Most recently, Sara has been working on analyzing different intervention strategies for Pandemic Influenza.

Phillip Stroud has been on the technical staff at Los Alamos National Laboratory since 1984. He has designed, analyzed, and simulated systems relating to fusion power, strategic defense, theater missile defense, human decision-making behavior, anomalous aerosol detection, and disease spread.

Jane Riese is a Software Engineer working with the Los Alamos National Laboratory High Performance Computing Group. She joined the EpiSimS team in 2004.

Stephen Sydoriak is a computer programmer with the Los Alamos National Laboratory High Performance Computing Group. He has been working on the EpiSimS project for five years. His interests include the sub-location model, processor synchronization, disease description, and disease transmission.