

LA-UR- 07-3019

Approved for public release;
distribution is unlimited.

Title: PANDEMIC SIMULATION OF ANTIVIRALS + SCHOOL
CLOSURES: BUYING TIME UNTIL STRAIN-SPECIFIC
VACCINE IS AVAILABLE

Author(s): Susan M. Mniszewski, CCS-3
Sara Y. DelValle, Phillip D. Stroud, D-3
Jane M. Riese, HPC-1

Intended for: N. American Association for Computational Social &
Organization Sciences
June 7-9, 2007
Atlanta, Georgia



Los Alamos National Laboratory, an affirmative action/equal opportunity employer, is operated by the Los Alamos National Security, LLC for the National Nuclear Security Administration of the U.S. Department of Energy under contract DE-AC52-06NA25396. By acceptance of this article, the publisher recognizes that the U.S. Government retains a nonexclusive, royalty-free license to publish or reproduce the published form of this contribution, or to allow others to do so, for U.S. Government purposes. Los Alamos National Laboratory requests that the publisher identify this article as work performed under the auspices of the U.S. Department of Energy. Los Alamos National Laboratory strongly supports academic freedom and a researcher's right to publish; as an institution, however, the Laboratory does not endorse the viewpoint of a publication or guarantee its technical correctness.

Pandemic Simulation of Antivirals + School Closures: Buying Time until Strain-Specific Vaccine Is Available

S. M. Mniszewski, S. Y. Del Valle, P. D. Stroud, J. M. Riese, S. J. Sydorciak

LAUR-07-
Los Alamos National Laboratory
April 30, 2007

Abstract

A strain-specific vaccine is unlikely to be available in the early phases of a potential H5N1 avian influenza pandemic. It could be 3-8 months before a vaccine is available and at the current production rate of 3-5 million doses per week may not provide timely protection to the population. Intervention strategies that control the spread of infection will be necessary in this situation. Such a strategy is the use of the US stockpile of antiviral medication coupled with a 6-month school closure. The agent-based simulation model, EpiSimS, was used to assess the impact of the intervention strategy of antivirals and school closures with 3 different vaccine approaches: 1) 2-dose, 80% effective, 2) 1-dose, 30% effective, and 3) 1 dose, 80% effective. This strategy can reduce the transmission of the disease and prolong a pandemic, though a second wave is generated during vaccine distribution once school closures are relaxed. Some of the benefits of these interventions can be lost when followed by a less than ideal vaccine approach. Simulations show that antivirals and school closures could slow influenza spread and reduce morbidity and mortality while in effect. A significant second wave can occur with current vaccine technology, though an ideal vaccine is able to contain it. Advances in vaccine development enabling increased production rates could alleviate this effect. School closure could be an important tool for delaying a pandemic. However, planning will be required to develop procedures that ensure continuity of instruction.

Introduction

Slowing the spread of influenza pandemic is all that can be done until large supplies of antivirals and vaccine are available for treatment and prevention. The latest avian influenza classified as H5N1 is threatening the globe as the future influenza pandemic [Holmes 2005]. The rapid spread of influenza, its short incubation period, lack of early effective vaccines [Fedson 2003], and increased air travel pose a significant challenge to the design of useful intervention strategies.

Antivirals could potentially 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]. However, there are insufficient antivirals stockpiled to provide adequate long-term prophylaxis for the entire population, or even for high-risk populations. 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 2006a]. Non-pharmaceutical interventions such as school closures will be necessary until adequate supplies of vaccine and antivirals are available [World Health

Organization Writing Group 2006]. The use of antivirals could begin early in a pandemic prior to the establishment of non-pharmaceutical measures.

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]. Interventions targeting children such as school closures could prove beneficial.

The Center for Disease Control and Prevention (CDC) has issued guidelines that will help slow the spread of the next pandemic until vaccines become available including non-pharmaceutical interventions such as home quarantine and closing schools [CNN 2007]. Historically, behavioral modifications have been used to reduce the spread and halt many epidemics. For example, seven communities used protective sequestration during the second wave of the 1918 influenza pandemic in order to prevent infection [Markel 2006]. Another example of unintended behavioral changes 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 on seasonal influenza morbidity [Heymann 2004].

School closures were observed during the SARS outbreak, which helped control its spread [Pang 2003]. Therefore, it is crucial to assess the impact that non-pharmaceutical interventions could have on future disease spread and how they can be optimized [Del Valle 2005]. Several studies have evaluated the impact of behavioral changes such as school closures, under different scenarios for pandemic influenza [Ferguson 2005, Germann 2006, Colizza 2007]. Most of these studies have assumed that these behavioral modifications would remain in effect for the duration of the pandemic. Furthermore, the CDC has recommended closing schools from one to three months if the next pandemic is similar to the 1918 influenza pandemic [CNN 2007].

Egg-based production of influenza vaccine in the United States is currently 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]. It is assumed that 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]. One study shows that administering a single dose vaccine with about half the protection of two doses to twice as many people can be more useful than two doses when supplies are limited [Germann 2006]. Other approaches are being explored to increase vaccine production, such as adjuvants for reducing the amount of antigen required per dose, use of live attenuated influenza vaccine, whole-virus based inactivated vaccines, and cell-culture production [World Health Organization 2006]. These technology developments might reduce the lag time between identification of the influenza strain and initial availability of vaccine, and might also allow higher US production rates. An ideal vaccine would require only one dose per individual for protection with a high efficacy.

This study assesses the impact of a combined intervention strategy of administration of the 6.7% stockpile of antivirals to sick individuals and their household members coupled with a 100% school closure to slow the spread of an influenza pandemic until strain-specific vaccine becomes available.

Methods

We used the epidemic simulation engine EpiSimS [Barret 2005, Eubank 2004, Del Valle 2006, Stroud 2006] 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. In brief, EpiSimS is an agent-based 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. EpiSimS simulations were run with a synthetic population constructed to statistically match the 2000 population demographics of southern California at the census tract level. The synthetic population consists of 18,828,569 million individuals living in 6 million households, with an additional 938,000 locations representing actual schools, businesses, shops, or restaurant addresses. Each individual in the simulation is assigned a schedule of activities to undertake throughout the day. Each individual's schedule specifies the starting and ending time, the type, and the location of each assigned activity. 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]. From these three components (synthetic population based on census data, business locations based on business directory data, and activity schedules based on the National Household Transportation Survey data), EpiSimS computes which individuals are together at the same location at the same time.

The number of people at various locations and at various times 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* 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 *location* will be sub-divided into *classrooms* and workroom sizes are set according to standard industry classification (SIC codes). The households on a city block are represented as a single geographically-located *location*, which is divided into separate *rooms*, each representing individual households. EpiSimS integrates all of this information into a computer model in order to simulate disease transmission for large human populations.

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 [Ferguson 2005]. The model consists of five main epidemiological stages: uninfected, latent (non-infectious), incubation (partially infectious), infectious, and recovered. The infectious class is sub-divided into three states: sub-clinical infectious (33% of the cases), symptomatic non-circulating (33%), and symptomatic circulating (33%). We assume that individuals in the sub-clinical state are half as infectious as the symptomatic individuals and people in the symptomatic non-circulating state are the fraction of the population that self-isolates at home. EpiSimS takes that 50% of adults and seniors, 75% of students, and 80% of pre-schoolers will stay at home within 12 hours of the onset of influenza symptoms. Furthermore, we assume that if a child under the age of 12 self-isolates, an adult will stay at home with the sick

child until he or she recovers or dies. The incubation period for influenza has been reported to be from 1 to 3 days with a mean of 1.9 days, which is slightly longer than the latent period. Based on Longini et al. [Longini 2004], we assumed an interpolated half-day interval histogram with mean 1.9 {0, 0.12, 0.18, 0.259, 0.238, 0.13, 0.07, 0.003}, giving respectively the fraction of cases that incubate for a period of between 0 and 0.5 days, 0.5 and 1.0 days, etc. before transitioning to the symptomatic stage. The infectious period ranges between 3 to 6 days with mean of 4.1 days. Thus, we assumed a half-day interval histogram with mean 4.1. The symptomatic stage sojourn time distribution is described by the histogram {0, 0, 0, 0, 0.005, 0.125, 0.16, 0.205, 0.205, 0.12, 0.08, 0.06, 0.04}, giving the fraction of cases that are symptomatic for 0 to 0.5 days, 0.5 to 1.0 days, etc. To simulate the higher attack rates seen in children, we assume that the infection rate in children was double that in adults. The model was used to analyze the potential impact that the administration of stockpile antivirals and school closures can have on influenza spread until strain-specific vaccine is available.

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, 5% will refuse. Those receiving prophylaxis that are exposed during treatment have a 20% chance of becoming infected. In this study, it is assumed that there are only enough antiviral courses available for 6.7% of the population based on the U. S. stockpile.

Protection of children is important in a pandemic, because illness rates are typically highest among school-aged children. Closing schools limits their contacts and exposure to potentially infected classmates and can block paths of spread between families and neighborhoods [Ackerman 1984]. School closures in EpiSimS are implemented as a general closure of selected activity locations. Based on the CDC pandemic guidelines [CNN 2007], closures follow a step-like function and are specified in EpiSimS with a start and stop time, the activity to close, 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. Given the fraction of schools that the analyst wants to close, schools are chosen at random from the six counties in southern California. In this study 100% of the schools are closed for 6 months starting when 0.1% of the population is symptomatic (day 53), intentionally overlapping vaccination delivery.

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. This assumes that a limited number of vaccines, 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. 95% of the selected household members are vaccinated, 5% refuse.

Three vaccine approaches were considered. The first approach 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 inoculated persons that don't develop immunity become infected, they would be only one fifth as

infectious as their unvaccinated counterparts. The second vaccine approach is a per person course of a single dose of the first vaccine, providing 30% seropositivity after 14 days [Lin 2006], assuming 30% become immune. The third is an ideal single dose vaccine, providing 80% seropositivity after 14 days. Every unvaccinated household has an equal chance of receiving the next available course.

Tabulations of epidemic parameters, new infections per activity, and worker absenteeism are collected for each simulation scenario. The epidemic parameters include daily counts of new infections, symptomatics, mortality, etc. overall or 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) are assembled, along with the cumulative days lost.

Results

Based on evidence from the three pandemics that occurred during the 20th century, scientists have determined that pandemic flu strains tend to infect between 25% and 35% of the population. The homeland security council has released the national strategy for pandemic influenza for the U.S, and it 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]. Thus, 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 \mathcal{R}_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.

Epidemic

Our study shows that antivirals + school closures provide 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. For these scenarios, it is assumed that schools close when 0.1% of the population is symptomatic (day 53) and they remain closed for 6 months. The first wave is defined as the first 183 days when antiviral and school closures are active. This includes some vaccination delivery beginning around day 150. The second wave runs from day 184 till the end of the epidemic and represents time when only vaccination is available. 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. Antivirals + school closures for 6 months reduces the clinical attack rate to 1% and a loss of up to 10 lives per 100,000 persons during the first wave. The second wave is dependent on the vaccine approach. Even with a 2-dose vaccine the clinical attack rate is reduced from baseline. The 1-dose 30% effective vaccine performs similarly, though mortality is lower.

	Clinical Attack Rate %		Mortality per 100,000	
	1 st wave	2 nd wave	1 st wave	2 nd wave

Baseline	30.6	-	614	-
2-dose, 80% effective	1.1	20.9	9	385
1-dose, 30% effective	1.3	20.6	10	294
1-dose, 80% effective	1.0	0.1	8	1

Table 1. Epidemic results for antivirals + school closure interventions followed by different vaccine approaches.

Nearly half the population is vaccinated with 1-dose vaccines in the second wave as seen in Table 2. Antivirals for around 3% of the population are used in the first wave. All the antivirals are used up in the second wave for the 2-dose and 1-dose (30% effective) vaccine approaches by day 323 and 327, respectively. The ideal vaccine approach only uses antivirals for an additional 0.3% of the population in the second wave and results in an overall mortality rate of 9 per 100,000, comparable to 12 deaths per 100,000 for a US flu season.

	% of Population Receiving Treatments			
	Antivirals		Vaccine	
	1 st wave	2 nd wave	1 st wave	2 nd wave
Baseline	-	-	-	-
2-dose, 80% effective	2.5	4.2	3.8	21.5
1-dose, 30% effective	3.1	3.6	12.9	47.7
1-dose, 80% effective	2.4	0.3	12.9	47.6

Table 2. Treatments used for antivirals + school closure interventions followed by different vaccine approaches.

In Figure 1A-D the symptomatic percentage of the population as a function of time is shown for the baseline and antivirals + school closure scenarios. School closures are relaxed after 6 months due to the availability of a strain-specific vaccine. However, given the slow delivery rate of vaccine courses, a second wave of cases appears. Our results show that an antivirals + school closure scenario can effectively delay the spread of a pandemic until vaccine is available. The administration of vaccine extends the epidemics to nearly 500 days, more than 2.5 times the duration of the baseline scenario.

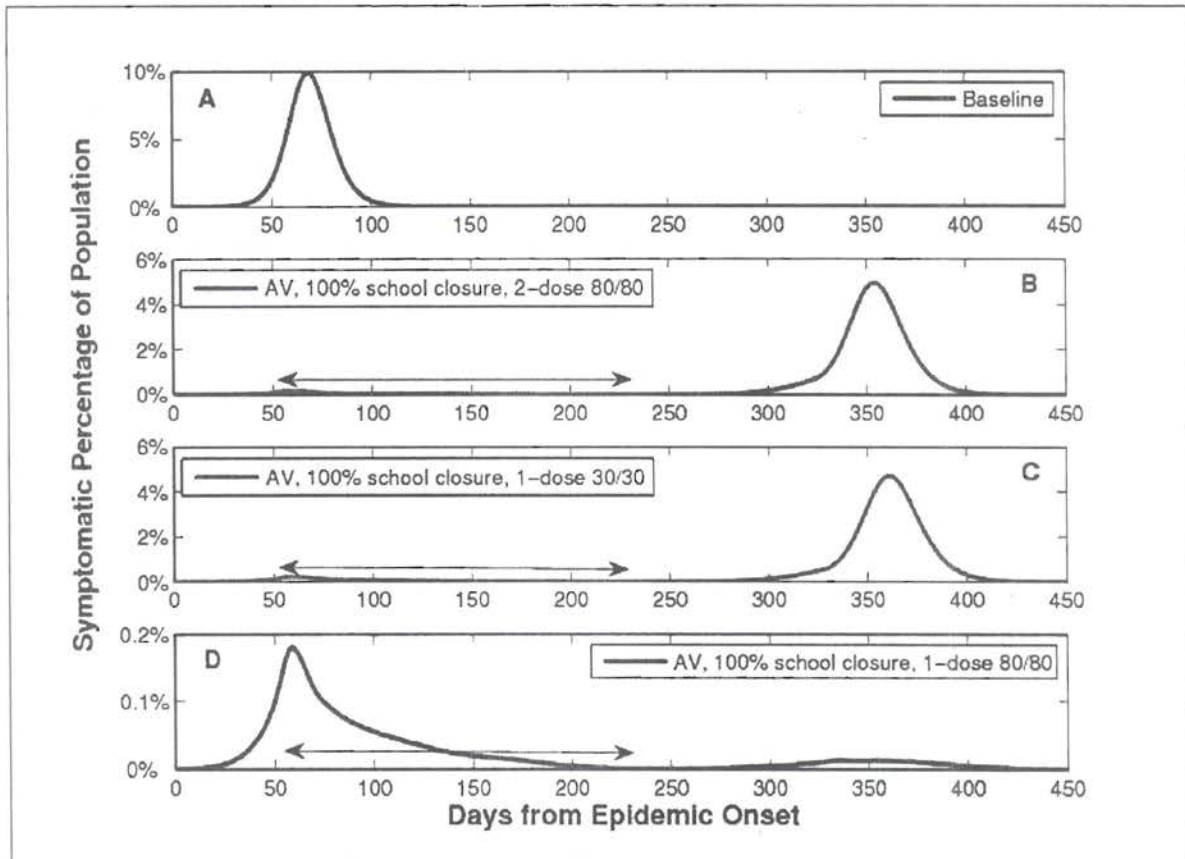


Figure 1. Symptomatic percentage of the population as a function of time for the baseline and antivirals + school closure scenarios: (A) shows the simulated epidemic curve for the baseline, (B) shows the results for antivirals + 6-month 100% school closure followed by a 2-dose 80% effective vaccine scenario, (C) shows the results for antivirals + 6-month 100% school closure followed by a 1-dose 30% effective vaccine scenario, and (D) shows the results for antivirals + 6-month 100% school closure followed by a 1-dose 80% effective vaccine scenario. The arrow shows when school closures are in effect. Note that as the interventions are relaxed (schools re-open) new infection waves appear.

Activity

Table 3 shows the percentages of new infections based on the population that occur during home, work, and school activities by wave. In the first wave, new infections are kept low across all activities. New infections increase in the second wave, most significantly at home. The overall percentages are still less than baseline. The ideal vaccine approach provides the best results, keeping new infections lower in the second wave activities than in the first.

	% of Population Infected by Activity					
	Home		Work		School	
	1 st wave	2 nd wave	1 st wave	2 nd wave	1 st wave	2 nd wave
Baseline	26.83	-	5.97	-	6.10	-
2-dose, 80% effective	0.81	18.23	0.30	4.11	0.12	4.48
1-dose, 30% effective	1.02	17.82	0.35	4.03	0.15	4.55

1-dose, 80% effective	0.78	0.10	0.28	0.02	0.13	0.05
Table 3. Results for infected percentage of population by activity.						

Worker Absenteeism

Table 4 shows the peak percentage of worker absenteeism and cumulative days absent per worker for each wave. The worker absenteeism peak typically follows the epidemic peak by a few days in an EpiSimS simulation. Antivirals + school closures reduce peak worker absenteeism to about 3% from 8% for the baseline in the first wave, though cumulative days lost has gone up to 5 days. In the first wave, worker absenteeism is mostly because of parents staying home with children due to illness or school closure. In the second wave most absenteeism is due to worker illness. The 2-dose vaccine approach causes a larger second peak due to less people having been vaccinated. The ideal vaccine keeps worker absenteeism in the second wave quite low.

	Worker Absenteeism			
	Peak %		Cum Days	
	1 st wave	2 nd wave	1 st wave	2 nd wave
Baseline	7.97	-	2.79	-
2-dose, 80% effective	2.92	4.10	5.14	1.88
1-dose, 30% effective	2.96	3.89	5.18	1.83
1-dose, 80% effective	2.93	0.02	5.15	0.03
Table 4. Results for peak worker absenteeism and cumulative absent days per worker.				

Discussion

A strain-specific vaccine will become available 3 to 8 months after the emergence of a new pandemic influenza and present production capabilities are insufficient to cope with the demand. The currently available stockpile of antivirals coupled with school closures could potentially delay the spread of a pandemic until vaccines become available. An agent-based simulation model with a highly structured population was used to demonstrate that this intervention strategy can have a significant effect on slowing influenza spread and reducing morbidity and mortality. However, the results show that some of the benefits of these interventions can be undone when followed by a less than ideal vaccine approach.

The simulations show that when 100% of the schools remain closed for 6 months along with therapeutic and prophylactic treatment with antivirals, the clinical attack rate can be reduced to 1%, well below baseline. However, if schools re-open before enough people have been vaccinated effectively, a second wave is likely to appear and the number of cases will increase. Thus, the CDC policy of school closures for 1 to 3 months [CNN 2007] may not guarantee success if the pandemic is still present. Even with two waves, the overall clinical attack rate was still lower than the baseline. Besides the benefits of reducing morbidity and mortality, this may reduce the impact on the healthcare system. The typical 2-dose 80% effective vaccine and the single dose 30% effective version were shown to give similar results with a 22% clinical attack rate, though 1-dose results in less mortality. Even at today's vaccine production rates, simulations have also shown that a 1-dose high-efficacy ideal vaccine is able to sustain

the clinical attack rate achieved with less than the national stockpile of antivirals and a 6-month school closure, results being comparable to seasonable flu.

There is an economic cost associated with the proposed intervention strategy, most notably due to a 6-month school closure. Simulation results show worker absenteeism being broken into two smaller waves and cumulative days lost per worker increasing by 2-4 days over an unmitigated pandemic. That is a small price to pay for reduced morbidity and mortality.

In principle, this pandemic intervention strategy of antiviral distribution and school closures followed by vaccine distribution has merit. Practically speaking though, care must be taken with the use of antiviral medication since evidence suggests that patients can develop resistance [De Jong 2005]. A distribution network must be available and allow for rapid dissemination of drugs to the population. Furthermore, school closures of 6 months will require the development of procedures to ensure continuity of instruction such as web-based distance instruction, mailed lessons and assignments, and instruction via radio or television [U. S. Department of Health and Human Services 2006b]. Additionally, current vaccine production requires interventions that will slow a pandemic as suggested in this study. Advances in vaccine development enabling earlier availability and increased production rates such as a cell-based approach could alleviate this constraint. The simulations here provide estimates of the effects of the recommended intervention strategies for future pandemic guidelines.

Acknowledgments

The authors would like to thank Deborah Kubicek for constructing the population data files used to set up the EpiSimS southern California synthetic population. Additionally, thanks to Andy White and the Institutional Computing Program at Los Alamos National Laboratory for providing access to the necessary supercomputing resources. This research has been supported through the NISAC project at Los Alamos National Laboratory under the Department of Energy contract DE-AC52-06NA25396.

References

Ackerman E, Elveback LR, Fox JP (1984) *Simulation of Infectious Disease Epidemics*. Springfield: Charles C. Thomas Publisher.

Barret, CL, Eubank SG, Smith JP (2005) If smallpox strikes Portland. *Sci Am* 292:54-61.

Carrat F, Sahler C, Rogez S, Leruez-Ville M, Freymuth F, Le Gales C, Bungener M, Housset B, Nicolas M, Rouzioux C (2002) Influenza burden of illness. *Arch Intern Med*. 162:1842-1848.

Colizza V, Barrat A, Barthelemy M, Valleron A, Vespignani A (2007) Modeling the Worldwide Spread of Pandemic Influenza: Baseline Case and Containment Interventions *PLoS Med* 4:95-109.

CNN (2007) CDC issues flu pandemic guidelines. Available:
<http://www.cnn.com/2007/HEALTH/conditions/02/01/flu.pandemic.ap/index.html>.
Accessed 20 February 2007.

De Jong MD, Thanh TT, Khanh TH, Hien VM, Smith GJD, et al. (2005) Oseltamivir resistance during treatment of Influenza A (H5N1) infection. *N Eng J Med* 353:2667-72.

Del Valle S, Hethcote H, Hyman JM, Castillo-Chavez, C (2005) Effects of behavioral changes in a smallpox attack model. *Math Biosc* 195:228-51.

Del Valle SY, Kubicek D, Mniszewski SM, Riese JM, Romero PR, Smith JP, Stroud PD, Sydoriak SJ (2006) EpiSimS Los Angeles case study. Los Alamos National Laboratory Unclassified Report 06-0666:1-81.

Eubank SG, Guclu H, Kumar VA, Marathe MV, Srinivasan A, Toroczkai Z, et al. (2004) Modeling disease outbreaks in realistic urban social networks. *Nature* 429:180-4.

Fedson DS (2003) Pandemic influenza and the global vaccine supply. *Clin Infect Dis* 302:1519-22.

Ferguson NM, Cummings DA, Cauchemez S, Fraser C, Riley S, Meeyai A, et al. (2005) Strategies for containing an emerging influenza pandemic in southeast Asia. *Nature*. 437:209-14.

Gani R, Hughes H, Fleming D, Griffin T, Medlock J, Leach S (2005) Potential impact of antiviral drug use during influenza pandemic. *Emerg Infect Dis* 11:1355-62.

German TC, Kadau K, Longini IM Jr, Macken CA (2006) Mitigation strategies for pandemic influenza in the United States. *PNAS* 103:5935-40.

Hayden F.G. (2001) Perspectives on antiviral use during pandemic influenza. *Phil Trans R Soc Lond B* 356:1877-84.

Heymann A, Chodick G, Reichman B, Kokia E, Laufer J (2004) Influence of school closure on the incidence of viral respiratory diseases among children and on health care utilization. *Pediatr Infect Dis J* 23:675-77.

Holmes EC, Taubenberger JK, Grenfell BT (2005) Heading off an influenza pandemic. *Science* 309:989.

Lin J, Zhang J, Dong X, Fang H, Chen N, Su N, et al (2006) Safety and immunogenicity of an inactivated adjuvanted whole-virion influenza A (H5N1) vaccine: a phase I randomized controlled trial. *The Lancet* 368:991-7.

Longini IM, Halloran ME, Nizam A, Yang Y (2004) Containing pandemic influenza with antiviral agents. *Am J Epidemiol* 159:623-33.

Markel H, Stern AM, Navarro JA, Michalsen JR (2006) A historical assessment of nonpharmaceutical disease containment strategies employed by selected U.S. communities during the second wave of the 19-18-1920 influenza pandemic. Defense Threat Reduction Agency Unclassified Report 01-03-D-0017:1-275. Available: <https://beta.saic.com/workshop/report/>. Accessed 20 February 2007.

Monto AS, (2006) Vaccines and antiviral drugs in pandemic preparedness. *Emerg Infect Dis* Vol. 12 No. 1 pp. 55-60. Available: <http://www.cdc.gov/ndidod/EID/vol12no01/05-1068.htm>. Accessed 15 February 2007.

Neuzil KM, Hohlbein C, Zhu Y (2002) Illness among schoolchildren during influenza season, effect on school absenteeism, parental absenteeism from work, and secondary illness in families. *Arch Pediatr Adolesc Med*. 156:986-991.

Pang X, Zhu Z, Xu F, Guo J, Gong X, Liu D, et al. (2003) Evaluation of control measures implemented in the severe acute respiratory syndrome outbreak in Beijing. *JAMA* 290:3215-21.

Stroud PD, Del Valle SY, Mniszewski SM, Riese JM, Sydoriak SJ (2006) Pandemic influenza impact analysis report: Simulations of disease spread and intervention effectiveness. Appendix A of The National Infrastructure Impacts of Pandemic Influenza: Phase 1 Summary Report, Los Alamos National Laboratory Unclassified Report 06-7066:1-80.

Tsolia MN, Logotheti I, Papadopoulos NG, Mavrikou M, Spyridis NP, Drossatou P, Kafetzis D, Konstantopoulos A, The Outpatient Flu Study Group (2006) Impact of influenza infection in healthy children examined as outpatients and their families. *Vaccine* vol. 24 (33-34), 5970-5976.

U. S. Department of Health and Human Services (2005) HHS Pandemic Influenza Plan. Available: <http://www.hhs.gov/pandemicflu/plan/pdf/HHSPandemicInfluenzaPlan.pdf> Accessed 20 February 2007.

U. S. Department of Health and Human Services (2006a) Antivirals – State Allocations. Available: <http://pandemicflu.gov/plan/states/antivirals.html>. Accessed 20 February 2007.

U. S. Department of Health and Human Services (2006b) School district (K-12) pandemic influenza planning checklist. Available: <http://www.pandemicflu.gov/plan/school/schoolchecklist.html> Accessed 21 February 2007.

U. S. Department of Transportation, Bureau of Transportation Statistics (2003) NHTS 2001 Highlights Report BTS03-05.

U. S. Government Accountability Office (2004) Flu vaccine: recent supply shortages underscore ongoing challenges. Available: <http://www.gao.gov/new.items/d05177t.pdf> Accessed 21 February 2007.

U. S. Homeland Security Council (2006) National Strategy for Pandemic Influenza – Implementation Plan. Available: http://www.whitehouse.gov/homeland/nspi_implementation.pdf. Accessed 20 February 2007.

Viboud C, Boelle PY, Cauchemez S, Lavenu A, Valleron AJ, Flahault A, Carrat F (2004) Risk factors of influenza transmission in households, *British Journal of General Practice*, 54, 684-689.

World Health Organization, Global pandemic influenza action plan to increase vaccine supply (2006) Available: <http://www.who.int/vaccines-documents/DocsPEF06/863.pdf> Accessed 20 February 2007.

World Health Organization Writing Group (2006) Nonpharmaceutical interventions for pandemic influenza, national and community measures. *Emerg Infect Dis* 12:88-94.