Pandemic Influenza and Complex Adaptive System of Systems (CASoS) Engineering

Robert J. Glass

Complex Adaptive Infrastructures and Behavioral Systems,
Sandia National Laboratories

P.O. Box 5800 MS 1138
Albuquerque, NM 87185-1138

Tel: (505) 8445606 Fax: (505) 284-3850

rjglass@sandia.gov

Abstract

I present the story of my and colleagues' involvement in formulating the US's policy for mitigating pandemic influenza that culminated in the Centers for Disease Control and Prevention's issuance of Interim Pre-Pandemic Planning Guidance in February 2007. Modeling lies at the heart of this formulation, but interaction, drive, serendipity, hard work, and advocacy for the use of models to select robust policy in the face of great uncertainty were required for its actualization. Reflecting on this entire process, and others in which high impact influence has been achieved, has led myself and colleagues to the recognition that nearly all the systems we wish to influence can be categorized as Complex Adaptive Systems of Systems or *CASoS* and that our field of endeavor is *CASoS Engineering*.

Key Words

pandemic, social network, complex adaptive systems of systems

1 INTRODUCTION

Before 2005, the US, and indeed the world, had little official policy, best practices, or even recommendations to implement in the face of a new, highly virulent strain of influenza that could rapidly advance around the globe as a pandemic of devastating proportions. Such deadly influenza pandemics have occurred many times in the past, most notably in 1918 when the Spanish Influenza killed many more people than died in concurrently raging World War I.[1] The known influenza strains that invade the US annually have evolved to be less virulent and can be

[1] World War 1 incurred 9-16 million deaths while estimates of the 1918 Spanish Influenza range to 50 million worldwide.

curbed using pharmaceutical measures such as vaccines and antiviral drugs.[2] Indeed, US public health measures to curb influenza in 2005 were entirely founded on these pharmaceutical measures. However, in the event of the eruption of a new strain, effective vaccine would not be available for 6 to 9 months[3], much longer than the likely time for the new strain to spread globally given today's highly connected world. Now in 2009, the US Centers for Disease Control and Prevention's (CDC) guidance for non-pharmaceutical community mitigation strategies forms the core of our national pandemic policy with Pandemic Preparedness Plans having been formulated at nearly every scale from the federal through state and local government, through business and industry, to schools and individual households (CDC, 2007). Although these plans must all be considered as "interim" due to the uncertainties associated with nearly every disease factor and its spread locally and across the globe, there is policy now where none previously existed. As the new H1NI strain dubbed "swine flu" has arisen to pandemic status in the summer of 2009[4], this policy is undergoing its first test and refinement.

Here, I recount the story of how I and colleagues contributed to and influenced the formulation of policy for the mitigation of influenza pandemics in the US. Because I tell this story from my own view, it is necessarily incomplete but hopefully conveys a sense of the efforts that I myself was involved in or knew about. At the core of our contribution were modeling and analysis but the actualization of the insights we gained through that effort required interaction, drive, serendipity, hard work, and advocacy for the use of models to select robust policy in the face of great uncertainty. The model that we designed, built, and applied to this problem and the string of resulting studies have been published in a series of papers beginning in 2005, with more to come; details of the model and our results may be found in these papers as referenced in the text below. The timescale for influence of public policy, however, was much shorter than the publication cycle and required active involvement in the process of its formulation.

The story really begins in 2003 when we began to build the capability for rapid modeling of infrastructure within the National Infrastructure Simulation and Analysis Center[5] (NISAC) at Sandia National Laboratories[6] (SNL). Our capability was abstracted from the science of complexity and combined simple local processes that generate emergent behavior at a larger scale (power laws in space and time) with complex networks, both features of nearly all

---

[2] Normal seasonal influenza results in the deaths of from 30 to 40 thousand people annually in the US alone, mainly among the elderly and immune-compromised.

[3] "A vaccine probably would not be available in the early stages of a pandemic… Once a potential pandemic strain of influenza virus is identified, it will take [six to nine] months before a vaccine will be widely available." [U.S. Centers for Disease Control, "Pandemic Influenza, Q&A," December 2005].

[4] On June 11, 2009, the World Health Organization (WHO) signaled that a global pandemic of novel influenza A (H1N1) was underway by raising the worldwide pandemic alert level to Phase 6. This action was a reflection of the spread of the new H1N1 virus, not the severity of illness caused by the virus. At the time, more than 70 countries had reported cases of novel influenza A (H1N1) infection and there were ongoing community level outbreaks of novel H1N1 in multiple parts of the world. From http://www.pandemicflu.gov.

[5] NISAC is a program under the Department of Homeland Security's (DHS) Preparedness Directorate. Sandia National Laboratories (SNL) and Los Alamos National Laboratory (LANL) are the prime contractors for NISAC under the programmatic direction of DHS's Office of Infrastructure Protection (IP), Infrastructure Analysis and Strategy Division (IASD).

[6] SNL is a multiprogram laboratory operated by Sandia Corporation, a Lockheed Martin Company, for the United States Department of Energy's National Nuclear Security Administration under contract DE-AC04-94AL85000.

infrastructure as well as human and biological interaction.[7] The story I recount in this paper focuses primarily on the period from the Fall of 2005 through the Winter of 2006 during which time we laid the foundation for and instigated the concept of Targeted Layered Containment (TLC). Following significant investment in a multi-pronged effort led by the US White House Homeland Security Council over the following year, TLC became integral to the CDC's Guidance released in February 2007 (CDC, 2007) that forms the basis of our current national pandemic policy. This containment approach, founded on non-pharmaceutical strategies that target the local social network on which influenza spreads, has been integrated into the guidance of the World Health Organization (WHO, 2009) and the policy of many countries around the world. And work continues.

Reflection on this entire process and others in which high impact influence has been achieved has led myself and colleagues to the recognition that nearly all the systems we wish to influence are Complex Adaptive Systems of Systems or *CASoS* and that our field of endeavor is *CASoS Engineering* (Glass et al., 2008). One of our aspirations is to control these systems through the formulation of policy whose choice is robust to uncertainty. To be successful, these robust policies must also be supported by incentives that sustain the critical enablers of system resilience. Identification and formalization of the process of CASoS Engineering has led to a new growing initiative, the *CASoS Engineering Initiative*.[8]

2 THE PANDEMIC STORY

PROLOGUE: In 2005, influenza A (H5N1), commonly known as "avian influenza" or "bird flu," became a matter of intense concern for public health officials world wide. From origins in Southeast Asia, H5N1 was spreading rapidly through domestic and wild populations of fowl: people in close contact with infected birds could become infected; over half of the people infected died. Luckily, H5N1 had not developed the ability to be passed from human to human at that time. As was known, forensic geneticists had established that the 1918 Spanish influenza virus (which killed over 50,000,000 people world-wide) required just a small set of critical mutations from its original avian form to jump species and allow human to human transmission. H5N1 already had achieved several of these mutations. We had a looming life or death problem of global proportion.[9]

TASKING: On Halloween 2005, NISAC received a call. Could we prepare a brief for Secretary Chertoff of the US Department of Homeland Security (DHS) as background for a cabinet level table top exercise at the White House? He and other Department Secretaries would be playing out possible strategies and their consequences in preparation for a potential impending influenza pandemic. The constraints on the exercise reflected the reality at the time: pandemic now; no vaccine; and extremely limited antiviral supplies[10]. What could we do to avert disaster? The

---

[7] See the NISAC-AMTI web site at : http://www.sandia.gov/nisac/amti.html.
[8] See the Sandia-CASoS website at: www.sandia.gov/casos.
[9] See http://www.avianinfluenza.org/mutated-avian-influenza-virus-h5n1.php for a thorough synopsis of H5N1 then and now.
[10] US had enough oseltamivir to treat 2.3 million people: http://www.cmaj.ca/cgi/content/full/173/7/743-a.

exercise would be conducted the second week of December, 2005: we had roughly a month to prepare our brief.

PREVIOUS EFFORTS 1: Over the preceding years, we had begun an effort at SNL-NISAC called the Advanced Methods and Techniques Investigations or AMTI.[7] The AMTI effort was to be a long-term investment in understanding critical infrastructures and their interdependencies. Our purpose was to identify and develop theories, methods, and analytical tools useful for understanding the structure, function, and evolution of complex, interdependent critical infrastructures (Glass et al. 2003). Critical Infrastructures are formed by a large number of components that interact within complex networks. As a rule, infrastructures contain strong feedbacks either explicitly through the action of hardware/software control, or implicitly through the action/reaction of people. Individual infrastructures influence others and grow, adapt, and thus evolve in response to their multifaceted physical, economic, cultural, and political environments. Simply put, critical infrastructures are *complex adaptive systems*. Complexity makes understanding and modeling critical infrastructures with classical means particularly difficult. Fortunately, there had been a great deal of basic research over the previous years focused on understanding complex adaptive systems and developing theories to explain how they behave under stress. We had begun to use this perspective in AMTI to reveal strategies that would make critical infrastructures more robust and/or resilient, and enable the formulation of long term policies whereby robustness and resilience could evolve over time.

REASONING BY ANALOGY: At the time, critical controlling aspects of power grid blackouts, financial crises, riots, species extinction, forest fires and many other cascading failures had been studied and explained with simple models of complex systems (e.g., Stauffer and Aharony 1992, Jensen, 1998). The spread of a pandemic exhibits many similarities to that of a forest fire: you catch it from your neighbors. To check a forest fire, such modeling had queried two diametrically opposed approaches: building fire breaks (checkpoints) based on where people throw cigarettes (border crossings) or thinning the forest so that no matter where a cigarette (infected person) is thrown, a roaring wildfire (epidemic) will not burn. The second approach is far preferable as cigarettes will always be thrown in unexpected places and sparks from a raging fire can jump the break. Because a pandemic runs on the interactions of people, the *social network*, we asked if the social network could be thinned reactively within each community as the pandemic rolled across the globe. If effective, the thinning could stop the spread locally and might even stop the ongoing roll of the global pandemic. This approach would not hamper the free movement of people and goods and, thus, would allow business to continue to operate within the globalized economy until a vaccine could be developed. It would also remove the imposition of quarantines at any scale, later so graphically documented in a movie made for TV[11]. The “thinning” approach makes use of our understanding of complex systems and applies this understanding to modify the social fabric of societies. Our *problem definition* became: Could we target the social network and take it apart intelligently so as to minimize social and economic impact?

[11] On Tuesday, May 9, 2006, at 8 p.m., the ABC television network aired a made-for-TV movie titled "Fatal Contact: Bird Flu in America." The movie follows an outbreak of the H5N1 avian flu virus from its origins in a Hong Kong market through its mutation into a pandemic virus that becomes easily transmittable from human to human and spreads rapidly around the world. See: http://www.pandemicflu.gov/news/birdfluinamerica.html#guide.

PREVIOUS EFFORTS 2: AMTI had developed the Loki toolkit for the rapid formulation and application of network models to complex systems. Loki is a set of computational objects that can be selected, specialized, and combined to create models of diverse networks including power systems, pipelines, social networks, and financial networks, as well as interactions among them. We had used Loki on two test problems with significant and rapid results: electric power grids and large value payment systems (Glass et al., 2004). Late in the 2004, my AMTI colleague Walt Beyeler implemented a disease transmission model within Loki and my collaborator and daughter Laura Glass, an Albuquerque High 9th grader at the time, adapted it to study the spread of influenza for her 2005 Science Fair project. Looking at communities of people as a network of nodes and links, Laura applied the Loki model to the spread of influenza within a social network. People were nodes, their interactions were links. Influenza would spread along these links from person to person. Together, Laura, Walt Beyeler, and I implemented a simplified version of the natural history of influenza within a model person (a simple susceptible-infected-recovered SIR model) and the probabilistic transmission across links dependent on the state of the disease in a person.

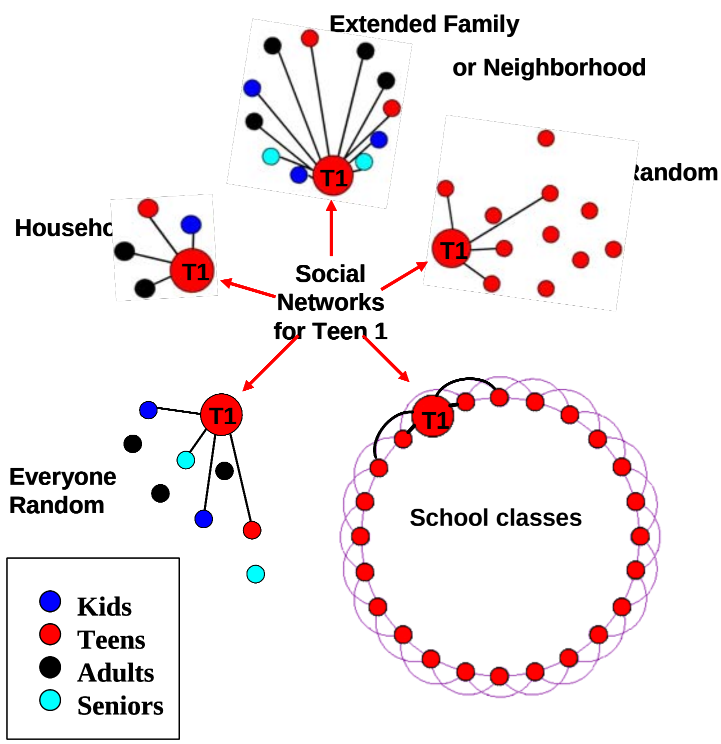

Figure 1: Example contact network

Groups and typical person-to-person links for a model teenager. The teenager (T1) belongs to a household (fully connected network, mean link contact frequency of 6 per day), an extended family or neighborhood (fully connected network, mean link contact frequency of 1 per day), and 6 school classes (ring network with connections to 2 other teenagers on each side, shown as black links; purple links denote connections of other teenagers within the class; mean link contact frequency of 1 per day). Two random networks are also imposed: 1 within the age group (teenager random, average of 3 links per teenager, mean link contact frequency of 1 per day) and 1 across all age groups (overall random, average of 25 links per person [not all links shown], mean link contact frequency of 0.04 per day). Figure 2 from Glass et al., 2006, but originally conceptualized as Figure 3 in Laura Glass's 2005 Intel Science Fair report.

To define the relationship links that people have, Laura asked a set of experts (e.g., moms with kids, kids at school, parents who work outside the home, the elderly) a series of questions: “what are your groups, how big are they, how often do you go to them and for how long, and how many people do you interact with there.” From this general information she constructed a social network for representative community members (see **Figure 1**) and combined them into a community of 10,000 people with multiple overlapping group sub-networks.

The representative community drew its members from the area surrounding a school within the larger city of Albuquerque, NM. By studying how influenza spread through the local community of 10000, Laura identified children and teens as the culprits and showed that vaccinating them alone was more effective at protecting the community then vaccinating adults or the elderly (see **Figures 2 and 3**).

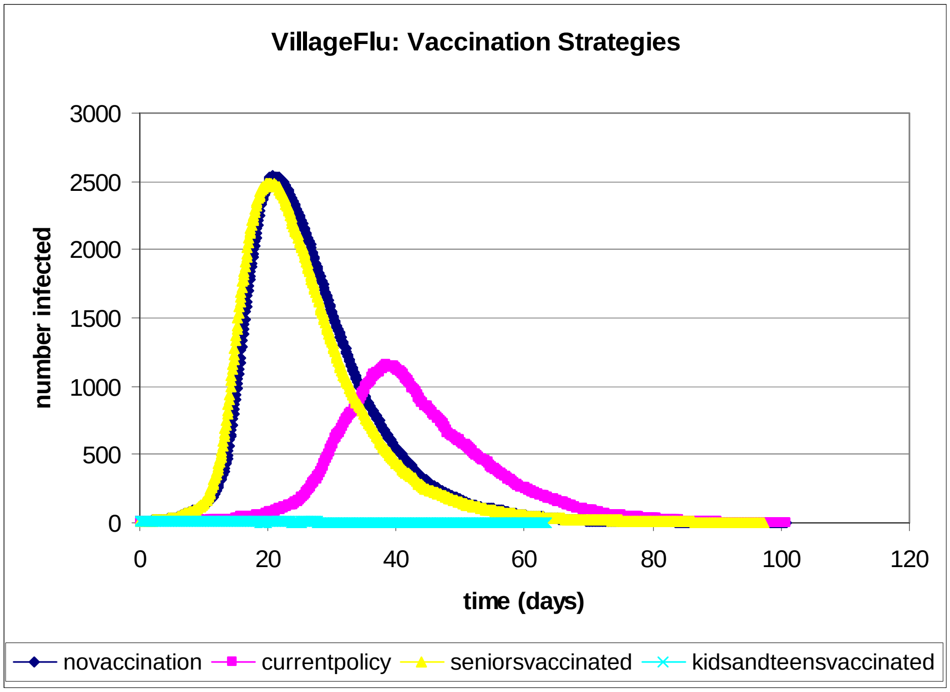

Figure 2: Influence of Vaccination Strategies on Epidemic.

Current policy implemented in years past averaged 26% vaccination for kids and teens, 30% for adults, and 59% for seniors. This policy is compared with vaccination of most seniors (90%) as they are the ones most likely to die and vaccination of most kids (90%) and teens (90%) as they are the ones that rapidly spread the disease to the most number of people. Figure 8 from Laura Glass’s 2005 Intel Science Fair report.

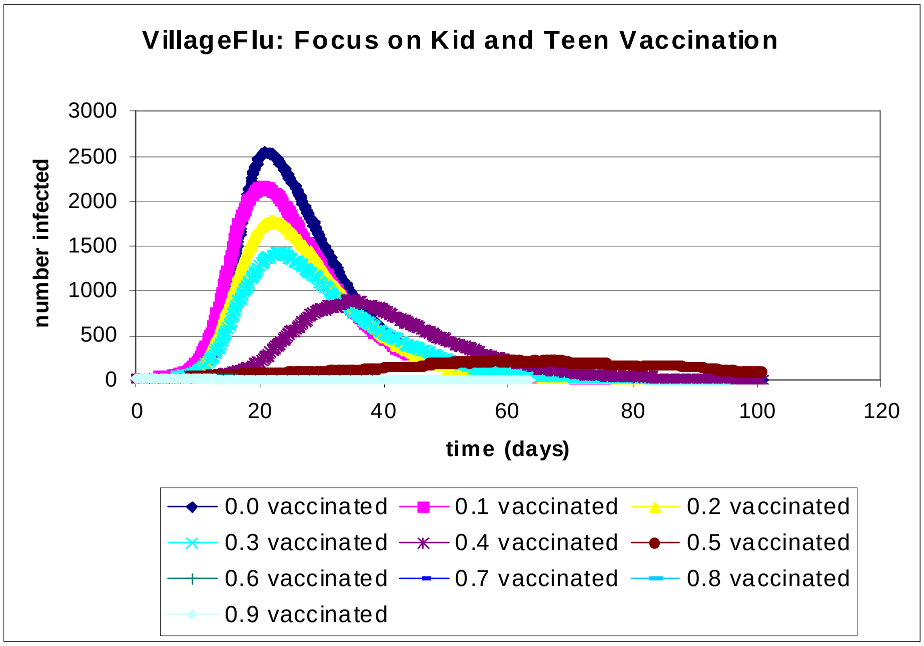

Figure 3: Influence of Vaccinated Fraction of Children and Teens on epidemic.

As the fraction of children and teens that are vaccinated increase, the severity of the epidemic decreases. For a 1958-like epidemic, herd immunity occurs at a fraction of approximately 0.6, thus protecting the entire population when only about 18% of it are vaccinated. Figure 10 from Laura Glass's 2005 Intel Science Fair report.

This result was of particular relevance due to the events of the Fall 2004 when the annual supply of vaccine presented a critical shortfall. The policy at the time was to first vaccinate those most apt to die if they became infected (elderly and immune-compromised individuals), a policy that did not protect the community (or those most apt to die) most effectively. A review of the literature at the time of Laura's study showed that this result was implied by a number of studies (e.g., Reichert et al., 2001), but hers was the first to find and evaluate it using a model. Laura went on to win the Grand Award at the New Mexico State Science Fair and take 4th place in Medicine and Health Sciences at the INTEL International Science and Engineering Fair in Phoenix, Arizona in April, 2005.

OUR INITIAL PANDEMIC ANALYSIS: Returning to the pandemic problem for DHS Secretary Chertoff, I ran Laura's model with a disease manifestation for influenza approximated from the literature and demonstrated that when tuned to the overall attack rate for the 1958 pandemic the model successfully predicted that pandemic's outcomes for the percentages of people of different age classes who were infected, suggesting that the node and link behavior, the network, and the combination, embodied representative "physics" for this problem. This level of model testing was standard for what others could and have done with their models of the ordinary differential equation, discrete stochastic, or agent-based varieties. However, all these other models and model types relied on parameters that were calibrated to the details of an actual epidemic (often many, many parameters!). Our model was based on informed approximations of the social network that anyone could give us (expert elicitation), simple assumptions for the relative effectiveness of transfer by age class (e.g., the effective transmission rate between children was assumed to be twice that between adults because of social interaction behavior), the basic disease manifestation and life history of influenza as could be obtained from clinical measurement and reported in the literature, and one parameter for the overall disease infectivity that was adjustable to yield a selected total number of people infected over the course of an epidemic (the attack rate).

With my daughter Laura, I then concentrated on taking the social network apart in an intelligent, targeted fashion that would minimize societal burden. I built on Laura's results and focused on children and teens: in which groups were they transmitting the flu? A careful analysis of the network of infectious contacts showed that children and teens form its backbone (see **Figure 4**) and identified schools as the primary transmission environment for children and teens (see **Figure 5**). We closed the schools in the model. If the kids and teens replaced school time with time spent hanging out and interacting at the mall, analysis showed that closing schools actually made things worse. But if these young people were kept primarily at home, the spread of a 1958-like pandemic could be eliminated within the community, and if compliance was 100% with the measure, even a 1918-like infectivity might be controlled (see **Figure 6**). Adults could continue to go to work with business as usual to keep the economy rolling. While incomplete, we had the makings of a simple straightforward *solution* on which to build.

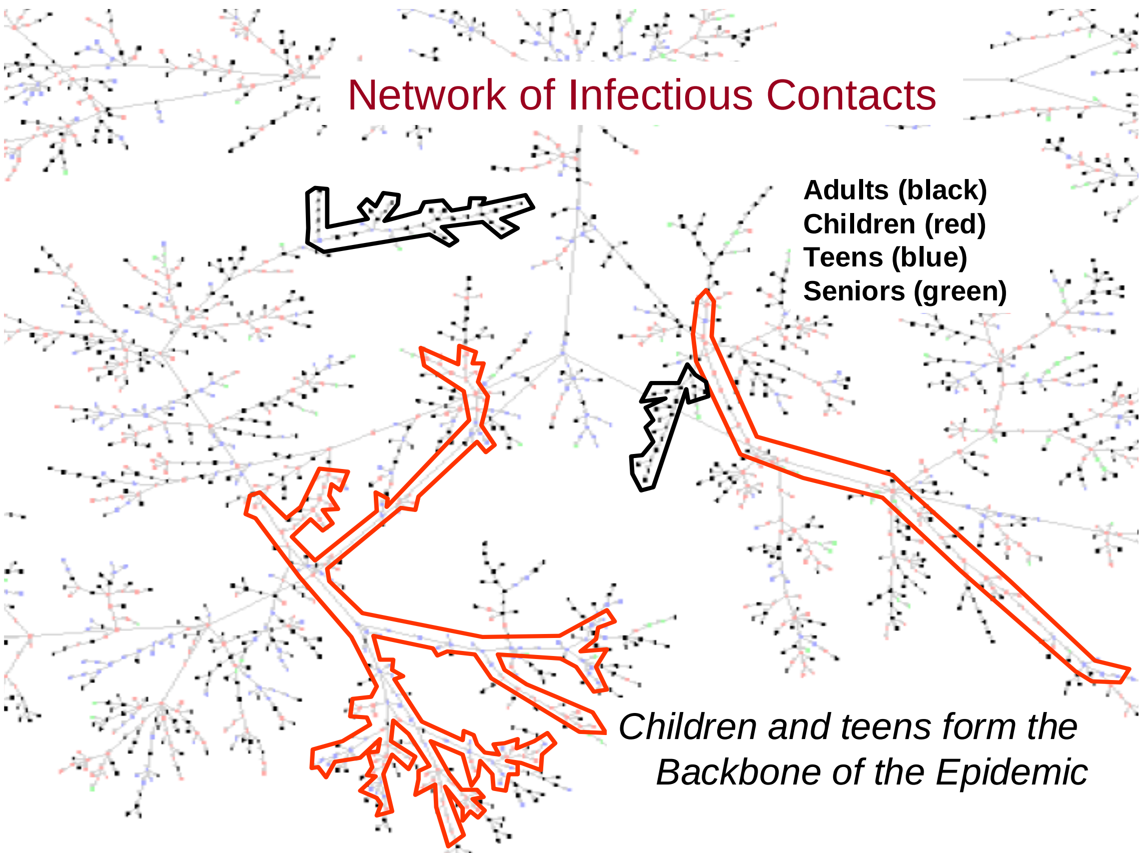

Figure 4: Network of infective contacts for an unmitigated epidemic.

Example zones outlined in red are composed of children and teens who form the backbone of the epidemic. Example zones outlined in black are composed of adults often within the work environment where the infective network stops growing. Figure 9 from Laura Glass's 2006 Intel Science Fair report. Outlining of red and black regions subsequently added by De. Hatchett, leader of the WH-HSC-PIP writing team.

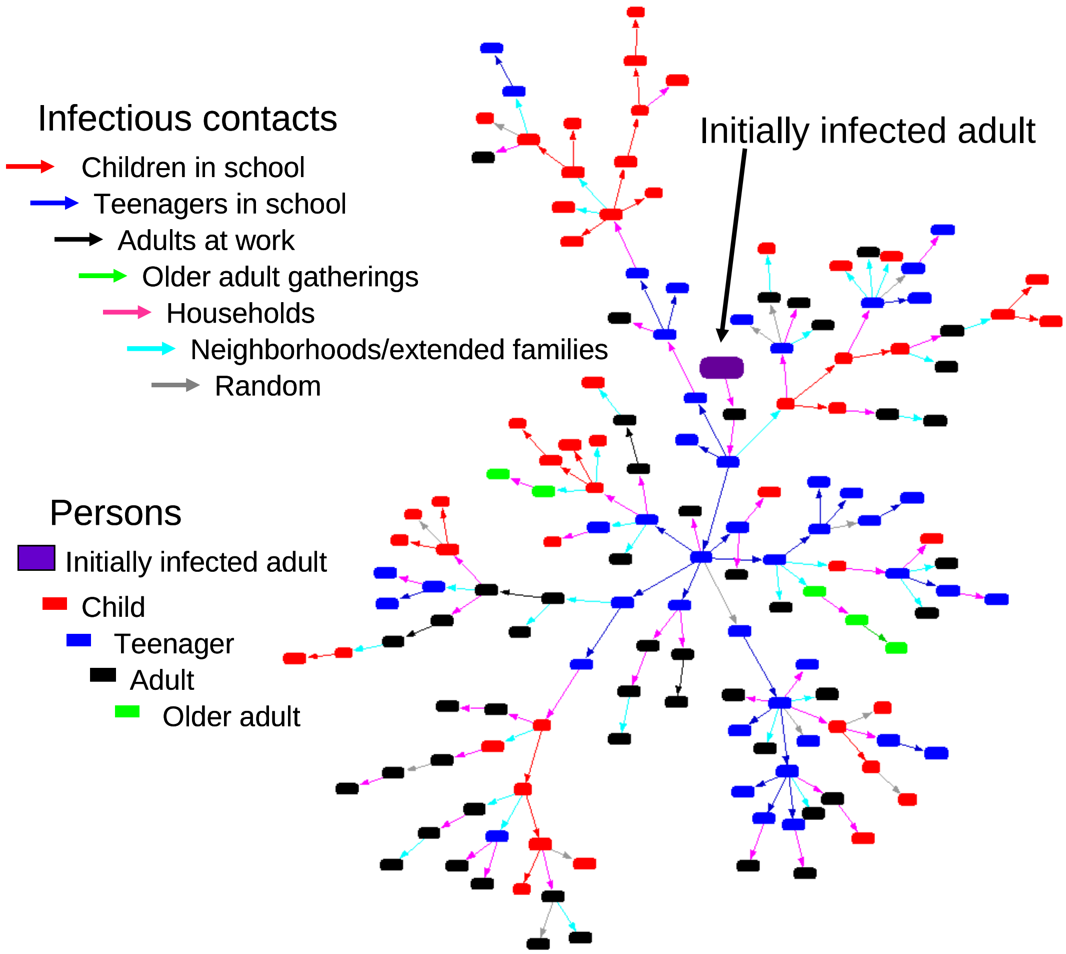

Figure 5. Initial Growth of the Epidemic.

Initial growth of an infectious contact network. Colored rectangles denote persons of designated age class, and colored arrows denote groups within which the infectious transmission takes place. In this example, from the adult initial seed (large purple rectangle), 2 household contacts (light purple arrows) bring influenza to the middle or high school (blue arrows) where it spreads to other teenagers. Teenagers then spread influenza to children in households who spread it to other children in the elementary schools. Children and teenagers form the backbone of the infectious contact network and are critical to its spread; infectious transmissions occur mostly in the household, neighborhood, and schools. Figure 10 from Laura Glass's 2006 Intel Science Fair report and Figure 4 from Glass et al., 2006.

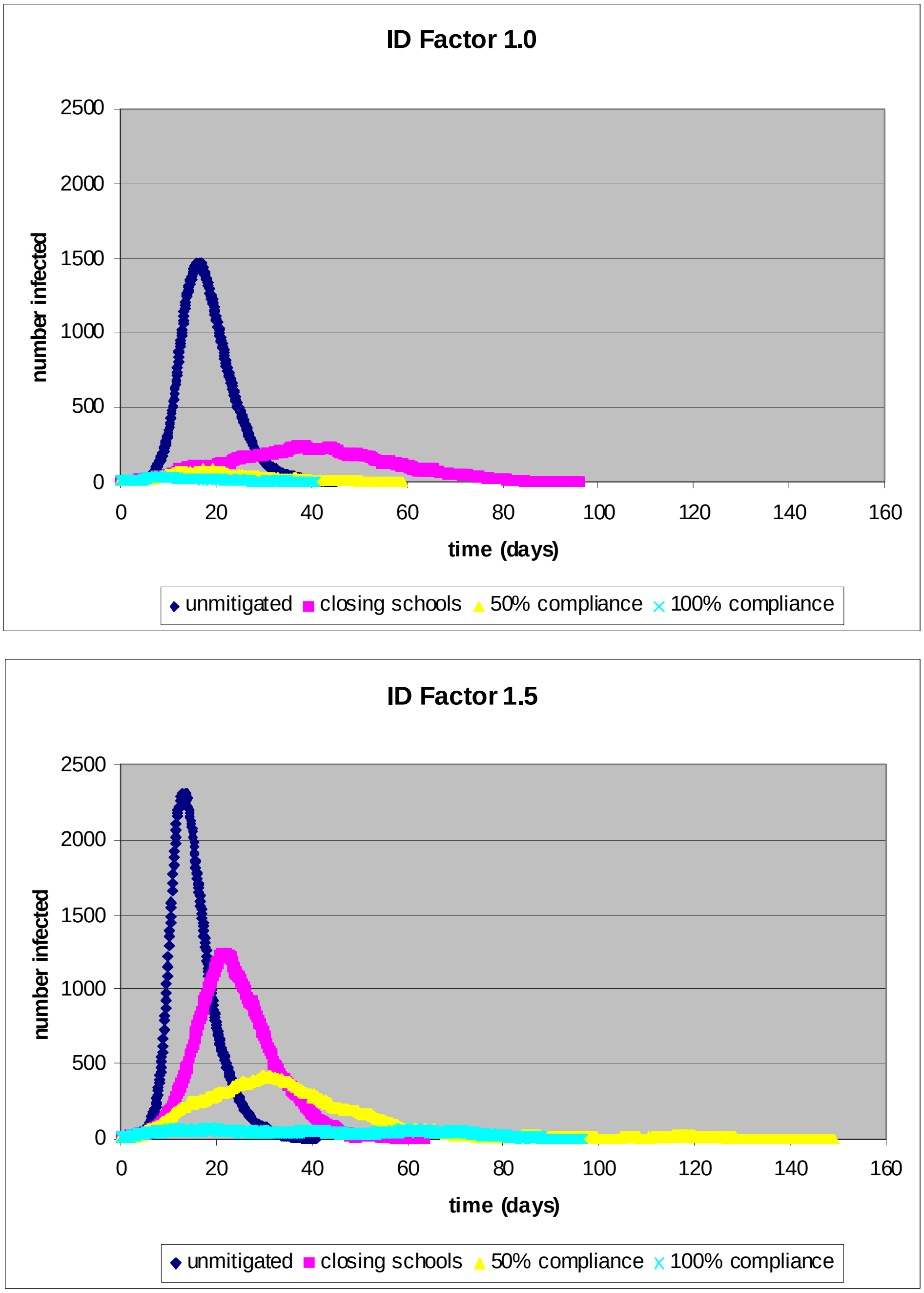

Figure 6. Targeted Social Distancing

Unmitigated (dark blue), closing schools alone (pink), closing schools and keeping children and teens at home with 50% compliance (yellow) and 100% compliance (light blue), for a 1958-like infectivity (top, ID Factor 1.0) and a 1918-like infectivity (bottom, ID Factor 1.5). Figure 11 and 12 from Laura Glass's 2006 Intel Science Fair report.

COMMUNICATING RESULTS THROUGH STANDARD PROFESSIONAL CHANNELS: I worked our results into two staged reports for Secretary Chertoff's briefing (Joint NISAC-CIP/DSS, 2005a, 2005b). However, these and other sources gave many, many other recommendations. The scenario within the tabletop exercise on December 10, 2005, directed discussion to the large scale spread of the disease (entry into the US and then movement along transportation routes within our borders) and the limitations of effective mitigation due to the fact that vaccine was not available and that antivirals were in very limited supply. Resulting from the exercise, a $7.1 billion request for emergency funding from Congress was introduced by the President to revitalize the pharmaceutical industry so that it could boost antiviral and vaccine production in the US.[12] But antivirals and were not currently available in quantity[10] and vaccine would inevitably require time to produce once a virus was identified.[3] As we had reasoned earlier through analogy with forest fires, trying to stop the large scale spread of the disease would inevitably fail and inflict devastating damage to the national and global economy. Our simple critical solution that targeted the social network at the community scale had not been heard. **Strike One.** I quickly wrote a Sandia report (much like a working paper at other institutions) and pushed it through review to allow unlimited pubic release (Glass et al, 2005a). I then submitted it to the rapid, high impact publication *Science*. Two weeks later it was rejected with the standard reply: "your manuscript was not given a high priority rating during the initial screening process … we feel that the scope and focus of your paper make it more appropriate for a more specialized journal." **Strike Two.** I then sought the help of high profile experts in the field, several of whom were getting their work in this field published quickly in *Science* (e.g. Longini et al., 2005). I sent our report to them with a cover letter explaining our results and asking if they would work with us to refine and publish jointly. They did not respond. **Strike Three**. It seemed we had struck out.

USING THE SOCIAL NETWORK: Professional standard channels had not worked. How was I to get our solution in front of the right people in the government, the ones who owned the problem? The government is a hierarchal institution whose operation is dictated by rules and protocol. But it is also composed of people with an informal social and influence network that stands apart from this hierarchy. I decided to use personal contacts and the social network. The previous summer at her aunt's house in Washington, DC, Laura had met Dr. Craig Hymes of the Department of Veterans Affairs (VA), Office of Public Health and Environmental Hazards. Dr. Hymes, an MD who also holds an MS in public health, had encouraged Laura to publish her study results. When I met Dr. Hymes later that summer he emphasized his encouragement of our work. We talked at length on the use of modeling within his world at the VA and the function of his Office: serendipitously, pandemics were under their purview at the VA. Maybe he could help. I sent our Sandia report to him and asked him to pass it on to whomever he thought should see it. He sent it immediately to nine colleagues, two of whom got back to me that day. These two contacts generated a set of intensive interactions along two separate but intertwined paths.

CRITICAL PATHS: The first path was through Dr. Carter Mecher, the VA's representative on the White House (WH) Homeland Security Council (HSC) Pandemic Implementation Plan (PIP) Writing Team. He responded immediately. This was the first thing he had seen that held a possible solution, wasn't just hand wringing over the lack of vaccine and pharmaceuticals. He sent it to Dr. Richard Hatchett, the team lead, and Dr. Hatchett contacted me. This was the first

[12] See press release: http://georgewbush-whitehouse.archives.gov/news/releases/2005/12/20051210-2.html.

thing that the he had seen that gave a direction and hope. I was then contacted by Dr. Rajeev Venkayya, the Senior Director for Biodefense Policy, HSC, and Special Assistant to the President for Biodefense: a meeting was scheduled for three weeks later when I would be in Washington DC on another project. The second path was through Vicky Davey, the Deputy Chief, Office of Public Health and Environmental Hazards (OPHEH) at the Veterans Administration (VA). Working on a doctorate degree at the Uniformed Services University of Health Sciences in addition to her normal duties, Vicky saw the usefulness of modeling in the formulation of policy. Vicky contacted me immediately. She wanted to define a set of critical issues surrounding the implementation of pandemic mitigation strategies and use our Loki model to evaluate them. We also set up a meeting while I would be in town.

OBTAINING HIGH LEVEL ACCEPTANCE: Over the next three weeks I worked evenings and late nights with the contacts at the WH-HSC-PIP to answer their questions on how the model worked, its foundations in the field of complexity, the modeling of complex systems, and the other problems to which we had applied the approach. Questions that arose during the day in their meetings would arrive via email or phone and I would respond, often modifying the model and setting off calculations that would hum away on my computer overnight.

- How sensitive were results to the social net? To disease manifestation?
- How sensitive to compliance? Implementation threshold? Disease infectivity?
- How did the model results compare to past epidemics and results from the models of others?
- Is there any evidence from past pandemics that these strategies worked?
- What about adding or "layering" additional strategies including home quarantine, antiviral treatment and prophylaxis, and pre-pandemic vaccine?

Meanwhile, Laura also continued her work. She found data within the literature for viral shedding and worked to represent it parametrically within the disease manifestation. She also revisited her formulation for the social network and, with additional expert solicitation, augmented the original base network with additional groups and details to see if they mattered. Over this short period we refined the model, roughed out its critical sensitivities, and defined the set of mitigation strategies for further evaluation. I then went to Washington DC and addressed the WH-HSC-PIP writing team. After a 4 hour presentation/interrogation/brain storming session in which many of the figures shown above were presented, we had changed the course of pandemic public policy and set a new direction.

POLICY ACTUALIZATION: Over the next year, an enormous amount of work was done across the nation that built on our results. While we continued to push with our model to answer questions such as those posed above, the WH-HSC-PIP instigated and coordinated a series of parallel efforts that laid the foundation for policy acceptance. Some of these efforts were:

- Our original report was expanded and published in the Centers for Disease Control and Prevention (CDC) online journal. This study included the accepted disease manifestation implemented by Laura and an evaluation of the influence of underlying social network topology and the base infectivity of the disease for effective design of targeted social distancing. For either an increased infectivity (to that of a 1918-like pandemic) or the unlikely proposition of equivalent transmission in each age class, it was shown that adults also needed to reduce their interactions within the community and at work for effective mitigation (Glass et al 2006). Laura, now in 10th grade at Albuquerque High, entered her parts of the analysis in the 2006 Science Fair where she once again won the Grand Award at the New Mexico State Fair and third place in Medicine and Health at the INTEL International Science and Engineering Fair in Indianapolis, Indiana in May, 2006.

- The concept of Targeted Layered Containment or “TLC” based on our results was socialized across a set of critical governmental departments and institutions (e.g., Department of Health and Human Services, the VA, Department of Education, Department of Homeland Security, National Institutes of Health (NIH), and the CDC). The WH-HSC-PIP integrated our figures and results into a persuasive presentation that conveyed the strategy and our approach for arriving at it in a way that their audience would understand and be convinced.
- Our results were evaluated and corroborated by modelers within the Models of Infectious Disease Agents Study (MIDAS) group funded by NIH. This group used several different modeling techniques to evaluate a suite of scenarios and mitigation strategy combinations that we helped the WH-HSC-PIP to design (Halloran et al., 2008).
- The triggers and whistles for implementing and rescinding community mitigation measures were systematically evaluated with Vicky Davey, the Deputy Chief Officer of OPHEH, as part of her PhD work. The best trigger was found to be no more than 10 diagnosed cases within the local community while the best rescinding whistle was 0 new cases within two reproductive periods of the virus strain. If cases did recur, strategies resumed at the 10 case trigger thwarted epidemic recurrence. (Davey et al., 2008a).
- The robustness of mitigation strategy policies to uncertainty and the identification of critical enablers of system resilience were also methodically evaluated with Vicky Davey. We systematically simulated a broad range of pandemic scenarios and mitigation strategies and evaluated illness and societal burden for alterations in social networks, illness parameters, and intervention implementation. For a 1918-like pandemic, the best strategy minimized illness to <1% of the population, combining network-based (e.g. school closure, social distancing of all with adults' contacts at work reduced), and case-based measures (e.g. antiviral treatment of the ill and prophylaxis of household members). We found the choice of this best strategy to be robust to removal of enhanced transmission by the young, additional complexity in contact networks, and altered influenza natural history including extended viral shedding. Administration of 50% effective pre-pandemic vaccine to 7% population (age-group or randomly targeted) coverage (current US H5N1 vaccine stockpile) had minimal effect on outcomes. In order of importance, mitigation success depends on rapid strategy implementation, high compliance, regional mitigation, and rigorous rescinding criteria; these are the critical enablers for community resilience (Davey et al., 2008b).
- Laura Glass developed a comprehensive survey-based method to characterize the social contact network for the potential transmission of influenza and then applied the method to school-aged children and teenagers in the Albuquerque School System. Results confirmed that high-school students may form the local transmission backbone of the next pandemic. Closing schools and keeping students at home during a pandemic was

shown to remove the transmission potential within these age groups and would thus be effective at thwarting influenza spread within a community. These results were entered by Laura in the College Boards's Young Epidemeology Scholars Competition in Spring 2007 and subsequently published in BioMed Central Public Health where it quickly became a "highly accessed" paper on their site (Glass and Glass, 2008).

- A comprehensive study two-year study of the influence of pandemics on critical infrastructure and the economy was conduced by NISAC. This study utilized many independent models that were applied to parts of the problem and integrated to yield an approximate picture (NISAC, 2007).
- A review of all modeling results was conducted by the Institute of Medicine (IOM) in October 2006 for independent evaluation. After listening to presentations by myself, the MIDAS modelers, and several others, the IOM issued a letter report supporting the implementation of TLC as interim policy for pandemic influenza (IOM 2006a,b).

On February 1, 2007 the CDC published its "Interim Pre-Pandemic Planning Guidance: Community Strategy for Pandemic Influenza Mitigation in the United States--Early, Targeted, Layered Use of Nonpharmaceuticial Interventions" (CDC, 2007) founded on our work and the concept of TLC: you can stop the transmission of a deadly virus by disrupting the social contact network on which the disease spreads. While many of the studies mentioned above did not reach publication ahead of the CDC's guidance, their results were made use of in the process. Work continues on community strategies for pandemic influenza mitigation that spans from research to policy formation to policy implementation, here in the US and across the globe. Now in 2009, with the rise of the novel influenza virus H1N1 reaching pandemic proportions, the guidance is being put to the test and refined as ambiguities are identified.

3 CASoS Engineering

In the summer of 2007, a group of staff at Sandia lead by myself and colleague Arlo Ames began to chart a roadmap for "Complex Adaptive Systems of Systems" or CASoS, initially as a way to pull together two separate scientific and engineering disciplines: "Complex Adaptive Systems" and "Systems of Systems". After a number of discussions that focused on definition, Arlo realized that what we were really interested in was influencing CASoS, solving problems within CASoS, or designing CASoS themselves. We all immediately agreed and the *CASoS Engineering Initiative* was born at Sandia (Glass et al., 2008).

The pandemic story presented above is an example of the type of problem and problem solving approach that we desire to formalize and then apply to systems ranging from the global energy system, to megacities, to health care networks, to just about every system that is important for human society, all of which are CASoS. For the pandemic influenza modeling, we were dealing with a large complex adaptive system, a CASoS: a global pandemic raging across the human population within a highly connected world (social, economic, political). The CASoS for the pandemic problem can be defined as:

- **System:** Global transmission network composed of person to person interactions beginning from the point of origin (within coughing distance, touching each other or surfaces)
- **System of Systems:** People belong to and interact within many groups households, schools, workplaces, they move within their environment at multiple scales (local to regional to global), and the policies of health care systems, corporations and governments place controls on interactions
- **Complex:** Many, many similar components (billions of people on the planet) and groups
- **Adaptive:** Each culture has evolved different social interaction processes, each will react differently and adapt to the progress of the disease, this in turn causes the change in the pathway and even the genetic make-up of the virus

The uncertainties in defining and modeling this CASoS seem overwhelming. But by analogy with other CASoS, their problems, their solutions, we defined the critical problem to solve (how to stop its spread locally with the least social and economic impact) and applied a generic approach for modeling and simulation (Loki's networks and agents). The questions that we then set out to answer were:

- What is the best mitigation strategy combination? (**choice**)
- How robust is the combination to model assumptions? (**robustness of choice to model uncertainty**)
- What is required for the choice to be most effective? (**critical enablers of system resilience**)

These three questions form the basis of nearly every CASoS Engineering problem and are central to our formalization of the *CASoS Engineering Framework*, a work in progress (Ames et al., 2009). The Framework is an attempt to capture the essence of past and current successful efforts, while avoiding pitfalls common to many modeling and simulation efforts. Development and refinement of the CASoS Engineering Framework is being accomplished through focus on high priority, specific applications while keeping an eye on general patterns that can provide high leverage to future activities.

While modeling lies at the heart of the policy engineering we conducted for the pandemic problem, the actualization of this policy required interaction, drive, serendipity, hard work, and advocacy for the use of models to select robust policy in the face of great uncertainty. Recognizing that the government itself is a CASoS, I used the social network to gain access to the critical people with influence; 2 degrees of separation between myself and people who owned the problem and 4 degrees of separation to the Senior Director for Biodefense Policy, HSC, and Special Assistant to the President for Biodefense. The WH-HSC-PIP were old hands at this game and used these same CASoS concepts (social network, influence network, critical people) to actualize the TLC policy in short time, roughly a year. The effort on everyone's part was immense; we were preparing to thwart the potential devastation of a deadly pandemic that could begin at any time. The engineering we were doing mattered, this was the type of problem that *CASoS Engineering Initiative* should address.

4 CONCLUSION

As scientists and engineers, we often wish that our work would have the impact that we believe it warrants. We are trained to do our research, write our papers, present them, publish them and then hope for impact. After many years of participating in this process, I believe this is not the approach we should always take (or be training students to always take). Much more is required for our work to influence the world around us. I have recounted the story of our involvement in influencing the US policy for response to an influenza pandemic in the formative period from the Fall 2005 through Spring 2006. This story combines modeling and the standard publication of results with the use of models to motivate and influence those who are actively working to formulate appropriate policy. Reflecting on this entire process in this and other applications has led myself and colleagues to a recognition that nearly all the systems that we wish to influence can be categorized as Complex Adaptive Systems of Systems or *CASoS* and that *CASoS Engineers* must do more than just the modeling to achieve their goals.

5 ACKNOWLEDGEMENTS

Many people played critical roles in the story I recounted here. Without them, our work would have gone nowhere. In the order of appearance they were: Walter Beyeler (SNL), Laura Glass (now Grinnell College), Dr. Craig Hymes (now FDA), Victoria Davey (VA), Dr. Carter Mecher (WH-HSC), Dr. Richard Hatchett (WH-HSC), Dr. Rajeev Venkayya (WH-HSC), Jason Min (SNL), Arlo Ames (SNL). Finally I must also thank Louise Maffitt (NMTech) for her expert help to convey this story with linguistic vigor.

6 REFERENCES:

Ames, A.L., R.J. Glass, W.E. Beyeler, et al., CASoS Engineering Framework and the Process of its Application, (SNL paper in review), 2009.

CDC: Interim Pre-Pandemic Planning Guidance: Community Strategy for Pandemic Influenza Mitigation in the United States--Early, Targeted, Layered Use of Nonpharmaceuticial Interventions, February, 2007. [http://www.pandemicflu.gov/plan/community/community_mitigation.pdf]

Davey, V.J., and R.J. Glass, Rescinding Community Mitigation Strategies in an Influenza Pandemic, ***Emerging Infectious Diseases***, Volume 14, Number 3, March 2008a. [http://www.cdc.gov/eid/content/14/3/365.htm]

Davey, V.J., R.J. Glass, H.J. Min, W.E. Beyeler and L.M. Glass, Effective, Robust Design of Community Mitigation for Pandemic Influenza: A Systematic Examination of Proposed U.S. Guidance, ***PLoSOne***, 3(7): e2606. doi:10.1371/journal.pone.0002606, 2008b. [http://www.plosone.org/article/fetchArticle.action?articleURI=info:doi/10.1371/journal.pone.0002606]

Glass, L.M., and R.J. Glass, Social contact networks for the spread of pandemic influenza in children and teenagers, ***BMC Public Health***, BMC Public Health, 8:61, doi:10.1186/1471-2458-8-61, February 14, 2008. [http://www.biomedcentral.com/1471-2458/8/61]

Glass, R.J., W.E. Beyeler, S.H. Conrad, N.S. Brodsky, P.G. Kaplan, T.J. Brown, Defining Research and Development Directions for Modeling and Simulation of Complex, Interdependent Adaptive Infrastructures, 32 pages (SNL paper SAND 2003-1778P), 2003. [http://www.sandia.gov/nisac/docs/Complexity_research_plan.pdf]

Glass, R.J., W.E. Beyeler, and K.L. Stamber, Advanced simulation for analysis of critical infrastructure: Abstract cascades, the electric power grid and Fedwire, 18 pages (SNL paper SAND 2004-4239), 2004. [http://www.sandia.gov/nisac/docs/AMTICascadeModeling.pdf]

Glass, R.J., L.M. Glass, and W.E. Beyeler, Local Mitigation Strategies for Pandemic Influenza, (SNL paper SAND 2005-7955J), December 21, 2005. [http://www.sandia.gov/nisac/docs/NISAC_FluMitigationPaperWithFullSOMTables.doc]

Glass, R.J., L.M. Glass, W.E. Beyeler, and H.J. Min, Targeted social distancing design for pandemic influenza, ***Emerging Infectious Diseases***, Vol. 12, No. 11, November 2006. [http://www.cdc.gov/ncidod/EID/vol12no11/06-0255.htm]

Glass, Robert J., Arlo L. Ames, William A. Stubblefield, Stephen H. Conrad , S. Louise Maffitt, Leonard A. Malczynski, David G. Wilson, Jeffery J. Carlson, George A. Backus, Mark A. Ehlen, Keith B. Vanderveen, and Dennis Engi, Sandia National Laboratories: A Roadmap for the Complex Adaptive Systems of Systems CASoS) Engineering Initiative, Sandia National Laboratories SAND 2008-4651, September 2008.

Halloran ME, Ferguson NM, Eubank S, Longini IM Jr, Cummings DAT, et al. (2008) Modeling targeted layered containment of an influenza pandemic in the United States. Proc Natl Acad Sci U S A 105: 4639–4644.

Institute of Medicine, Workshop on Modeling Community Containment, October 25, 2006 - October 27, 2006a. [http://www.iom.edu/CMS/3793/37624/37630.aspx]

Institute of Medicine, Modeling Community Containment for Pandemic Influenza: A Letter Report, Released On: December 11, 2006b. [http://www.iom.edu/CMS/3793/37624/39066.aspx]

Jensen, Henrik J., Self-Organized Criticality: Emergent Complex Behavior in Physical and Biological Systems, Cambridge University Press, 1998.

Joint NISAC - CIP/DSS, Preliminary Results for Avian Influenza Analyses, November 18, 2005a.

Joint NISAC - CIP/DSS, Analysis of Avian Influenza Virus Issues for the Catastrophic Assessment Task Force (CATF) Table-Top Exercise, December 7, 2005b.

Longini IM Jr, Nizam A, Xu S, Ungchusak K, Hanshaoworakul W, et al. (2005) Containing pandemic influenza at the source. Science 309: 1083–1087.

NISAC, National Population, Economic, and Infrastructure Impacts of Pandemic Influenza with Strategic Recommendations. October, 2007. [www.sandia.gov/nisac/pandemic_influenza.html]

Reichert, Thomas A., Norio Sugaya, David S. Fedson, W. Paul Glezen, Lone Simonsen, and Masato Tashiro, The Japanese Experience with Vaccinating Schoolchildren against Influenza, N Engl J Med, Vol. 344, No. 12, March 22, 2001.

Stauffer, Dietrich and Amon Aharony, Introduction to Percolation Theory, Taylor & Francis, 1992.

WHO: Pandemic Influenza Preparedness and Response, 2009. [www.who.int/csr/disease/influenza/PIPGuidance09.pdf]