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October 10, 2008

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This work performed under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under Contract DE-AC52-07NA27344.

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October 2008

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Executive Summary

This study uses the Multi-scale Epidemiologic Simulation and Analysis (MESA) system developed for foreign animal diseases to assess consequences of nationwide human infectious disease outbreaks. A literature review identified the state of the art in both small-scale regional models and large-scale nationwide models and characterized key aspects of a nationwide epidemiological model. The MESA system offers computational advantages over existing epidemiological models and enables a broader array of stochastic analyses of model runs to be conducted because of those computational advantages. However, it has only been demonstrated on foreign animal diseases. This paper applied the MESA modeling methodology to human epidemiology. The methodology divided 2000 US Census data at the census tract level into school-bound children, work-bound workers, elderly, and stay at home individuals. The model simulated mixing among these groups by incorporating schools, workplaces, households, and long-distance travel via airports. A baseline scenario with fixed input parameters was run for a nationwide influenza outbreak using relatively simple social distancing countermeasures. Analysis from the baseline scenario showed one of three possible results:

1) the outbreak burned itself out before it had a chance to spread regionally,
2) the outbreak spread regionally and lasted a relatively long time, although constrained geography enabled it to eventually be contained without affecting a disproportionately large number of people, or
3) the outbreak spread through air travel and lasted a long time with unconstrained geography, becoming a nationwide pandemic.

These results are consistent with empirical influenza outbreak data. The results showed that simply scaling up a regional small-scale model is unlikely to account for all the complex variables and their interactions involved in a nationwide outbreak. There are several limitations of the methodology that should be explored in future work including validating the model against reliable historical disease data, improving contact rates, spread methods, and disease parameters through discussions with epidemiological experts, and incorporating realistic behavioral assumptions.

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1.0 Introduction

The risk from emergent contagious diseases and bioterrorism is of concern to public health decisionmakers. The presentation of H5N1 avian influenza (AI) in Southeastern Asia, SARS, and the anthrax attacks in the United States within the last 10 years illustrates the extent of the threat and its potential to strain health response efforts. Although local spread characteristics and the performance of individual countermeasures are somewhat understood, a better understanding is needed on:

1) The risks posed by emerging threats,
2) The distribution of impacts and spread characteristics from a nationwide outbreak, and
3) The speed and adequacy of response measures to a nationwide outbreak.

Modeling and simulation builds understanding and provides a method to improve response plans. A reliable epidemiological simulation model enables analysts to identify:

1) how a disease might spread through a vulnerable population,
2) the effectiveness of existing response plans,
3) gaps in response plans, and
4) potential improvements that can be made to address gaps.

Many different simulation models have been developed for examining specific aspects of this problem, but it is important to distinguish local or regional models from large-scale, national models. Local models enable detailed modeling of the effects on a specific “test-tube” population, the capabilities of a specific countermeasure (or a small set of countermeasures), and disease spread characteristics within that specific subset of people. Large-scale models are inherently different due in part to the increased number of

variables, such as the incorporation of many close-knit communities, short distance interconnections between neighboring communities, and long-distance interconnections between some communities. Large-scale models must differentiate behaviors among people in different communities and response measures implemented on a local, regional, or national scale. These complexities require complicated epidemiological models with large-scale computational assets. Throughout this document a distinction is made between local/regional and national-scale models because of these inherent differences. Existing national-scale models are either too simplistic to definitively model the effects of specific diseases and countermeasures across a well-defined population or too detailed, requiring exorbitantly long run times which limits the inherent variability in spread dynamics that should be incorporated.

The MESA system has proven to be a useful system for modeling and simulation of nationwide foreign animal disease (FAD) outbreaks and countermeasure architectures. MESA incorporates a flexible, scalable architecture that models each entity (i.e., farm/herd in the FAD model) individually and an extensible design that enables different entity types, response strategies, and regional variations to be modeled [MELIUS 06]. Entities in the model are grouped together at the county, state, or national level and they are only instantiated when a specific entity plays a role in disease spread, which enables MESA to simulate multiple nationwide FAD outbreak runs without requiring exorbitantly long run times. This also enables statistical analyses to be conducted on the output from the model to better understand the natural variability in spread for a given set of inputs. This paper examines the prospects of applying MESA to a human disease by developing a nationwide population database at the census tract level, simulating daily human

behavior, and injecting a contagious disease into the population to simulate spread. MESA has the capability to simulate a human disease since the parameters that currently exist in MESA for animal disease modeling can simply be mapped into human counterparts. A nationwide outbreak of influenza is simulated to assess the feasibility of applying MESA to a nationwide human disease outbreak.

This paper is divided into four parts. The first section describes a literature review of models currently being used to examine nationwide human epidemiology and the prospects of the MESA methodology relative to other modeling efforts. The second section describes the modeling approach adopted to apply MESA to human epidemiology and a baseline influenza scenario is instantiated in this section. The third section describes results from the baseline scenario. The fourth section draws conclusions from the results and the MESA approach and identifies areas of future work to improve the reliability of MESA applications on human diseases.

2.0 Literature Review

A lack of empirical outbreak data necessitates the development of simulation models to generate synthetic disease data and evaluate countermeasure architectures. Nearly all computational models that have been developed are based on basic SEIR models [LI 1995]. The SEIR model divides populations into susceptible (S), exposed (E), infected (I), and recovered/removed (R) states and models the transitions between these states using state transition probabilities derived from disease spread characteristics. The likelihood of disease transmission between an infected individual and a susceptible individual is often modeled by a contact probability (i.e., characterizing the likelihood that two individuals will be in contact with each other) and a transmission probability,

unique to the disease. The basic reproductive number (R_0) of a disease represents the number of new infections occurring from a single infectious individual and is used to derive the transmission probability. R_0 is the product of the average number of contacts while a host is infectious and the transmission probability per contact. Control measures can either decrease the likelihood that an infectious individual will have contact with a susceptible individual (i.e., masks, social distancing, or quarantines) or decrease the likelihood that if a contact takes place, transmission will occur (i.e., antiviral treatment or vaccinations). Most major epidemiological simulation models are based upon these simple disease transmission processes and therefore, the major differences in their implementations revolve around assumptions regarding populations, mixing behavior, disease control measures, and data sources used to populate the model.

The most comprehensive research collaboration of human infectious disease modeling was sponsored by the National Institutes of Health (NIH) and entitled Models of Infectious Disease Agent Study (MIDAS). MIDAS was a collaborative effort between universities, national laboratories, and NIH to develop multiple infectious disease models at multiple geographic scales [NIGMS 08]. NIH divided the goals of the MIDAS study into research investigations used to inform health related policy and informatics missions used to advance the state of the art in large-scale modeling. MIDAS research investigations focused on emerging diseases, identification of disease outbreaks, countermeasure effectiveness, and host/pathogen interactions. MIDAS informatics missions included development of large-scale computational resources, creating knowledge management tools, formulating analytical/statistical approaches, developing

model repositories, acquiring relevant data, and developing testing and validation approaches.

MIDAS included two Southeast (SE) Asia regional models developed primarily for the evaluation and identification of an emergent human strain of avian influenza (AI). [LONGINI 05] describes a SE Asia regional influenza model supported by the National Institute of General Medicine Studies (NIGMS) and the Ministry of Public Health Thailand. In this model Thailand census data was employed using schools, workplaces, households, and community activities for mixing and various control measures are evaluated including antivirals, pre-vaccinations, and quarantines. [FERGUSEN 05] describes a SE Asia regional influenza model and was supported by many groups including the NIGMS and the University of Hong Kong. Thailand census data was broken down into households, schools, workplaces, and community sites for mixing and various control measures are evaluated including antivirals, vaccinations, and social distancing. [FERGUSEN 05] also implemented a novel approach where the infectiousness of a disease varies by a function of time since latency ends. Both of these models were intended to simulate an influenza outbreak from an AI source in SE Asia, which is important for identifying an emerging disease outbreak and how to contain the disease at its source before it has an opportunity to spread beyond the region. However, both of these models are inadequate for modeling a nationwide human infectious disease outbreak throughout the United States because they are regional models based on short distance communications between villages and towns. The lack of long-distance spread mechanisms limits these models to only regional evaluations of outbreaks.

MIDAS also consisted of a city-based US model called EpiSims developed primarily for assessing the feasibility of modeling disease spread within a mid to large US city [NIGMS 08]. The model has been demonstrated with influenza and smallpox outbreaks in several US cities. EpiSims divided the 2000 US census data into schools, workplaces, shopping, and community activities for mixing and incorporated many different disease control measures. EpiSims spurred the development of a nationwide US disease model to assess the feasibility of modeling disease spread across the country. This effort culminated in EpiCast, which was a collaborative effort sponsored by the Department of Health and Human Services (HHS) and Los Alamos National Laboratory (LANL) [GERMANN 06]. EpiCast is truly a large-scale nationwide model of disease spread. It broke down the 2000 US census into 2,000 person "communities" consisting of households, day-care centers, schools, workplaces, and neighborhoods for mixing. EpiCast also incorporated airline travel survey data to simulate inter-city spread. Many different control measures were modeled in EpiCast. Because EpiCast is a complex model that simulates a broad range of interactions with a large number of entities, the model is run on a LANL supercomputer and a typical run takes several days to complete [LANL 08; CIVA 07]. The complexities of the model arguably make it the most comprehensive large-scale nationwide spread model currently being used for human infectious diseases. The model has been demonstrated on nationwide influenza outbreaks and other nationwide epidemics [NISAC-CIP/DSS 05; GERMANN 06]. However, it does have some important limitations. EpiCast simulates all interactions taking place between all people, regardless of whether or not those interactions are playing a role in an outbreak's spread. This leads to long run times, computational complexity, an inability to

batch many runs at once, and limited incorporation of natural variability in input and output.

Several other large-scale nationwide models have been developed, but they are much more limited than EpiCast. For example, IBM developed a model named STEM that used a graph representation to connect nodes (i.e., individuals, cities, counties, states, or any other entity) [IBM 05; ECLIPSE 07]. At each time step, each node in the network is visited and an underlying researcher-specified SEIR model evaluates the state of each node in the network as a disease is simulated through the system. STEM has a highly flexible architecture that enables regional or national models to be developed. However, this flexible architecture also reduces the degree of specificity in the model and therefore the model is not as realistic as EpiCast. Other nationwide spread models suffer from similar problems. Therefore, EpiCast truly represents the state of the art in nationwide human epidemiological modeling.

The MESA system offers a large-scale epidemiological modeling alternative that is highly realistic and has fast run times and Monte Carlo sampling that are not available in other models [MELIUS 06]. MESA is an agent-based model where each set of individuals (i.e., a farm of animals or a census tract of people) is an entity in the model. An extensible design enables different types of entities, response strategies, and regional variations to be modeled. MESA incorporates an SEIR model implemented at the entity level to simulate spread within a herd or group of individuals. Then spread methods (i.e., mixing) are implemented which create opportunities for a disease to spread beyond a given entity. An advantage that MESA offers over alternative approaches is that it allows entities to be grouped into higher geographic levels, such as the county, state, or national

level. Entities far from an outbreak are viewed in the model only in the aggregate (e.g., aggregated to the state or national level) and entities close to the outbreak are viewed in the model at a finer resolution (e.g., a specific herd that might become infected). Entities in the model are only instantiated once they play a role in the spread of the disease. This extensible design enables MESA to run much more quickly than other comparable large-scale models currently in use. As a result, MESA runs are batched which allows for a distribution of epidemic outcomes to be generated in a comparatively short run time period. Furthermore, uncertain input parameters can be specified as distributions and those distributions can be sampled within a model run, which allows natural variability and uncertainty in input parameters to be more directly incorporated. Other large scale models assume all inputs are fixed point estimates, which limits their ability to explicitly account for uncertainty and variability. The MESA model has been effective for simulating the spread of foot and mouth disease (FMD) and avian influenza through US animal populations, but the model's structure is adaptable to modeling the spread of an infectious disease through any population of entities [BATES 05; HULLINGER 06; 07]. Based upon this review of the literature it appears that MESA offers a computationally efficient alternative to existing large-scale human epidemiological models.

3.0 Modeling Approach

Before focusing on a specific approach, important characteristics that should be included in a nationwide human epidemiological model were identified. An effective nationwide epidemiological model should have the capability to perform an end-to-end analysis of a disease outbreak. At a minimum, it must include a national population database, realistic behavioral variables that affect disease spread, and relevant disease

parameters. It should also have the capability to incorporate interventions implemented at various times during the outbreak's evolution.

In order to develop an epidemiological model that accounts for these components we identified and characterized the variables and relationships that drive infectious disease spread through a population. An influence diagram (see **Figure 1**) characterized these variables and their interactions. An influence diagram is a means by which variables in a complex decision process are organized in order to better understand the process and identify potential risks and opportunities that must be accounted for if the process is to be modeled [CLEMEN 01]. In an influence diagram rectangles correspond to decision nodes[1], ovals correspond to uncertain nodes[2], and hexagons correspond to outcomes. Connections between nodes in an influence diagram show relationships between variables, where the value at a node located at an arrow's destination is dependent upon the value of the node at the arrow's origin. The influence diagram in **Figure 1** derived from related avian influenza modeling work [FISCHHOFF 06] and related WMD consequence models [DOMBROSKI 06]. The influence diagram was developed at sufficient resolution to document the process and identify important variables and their interactions, although each variable in **Figure 1** could be modeled at a finer resolution.

[1] In this case decision makers are assumed to be public health officials.
[2] Uncertainty in the process could be driven by variability within the process itself or the behavior of people within the process.

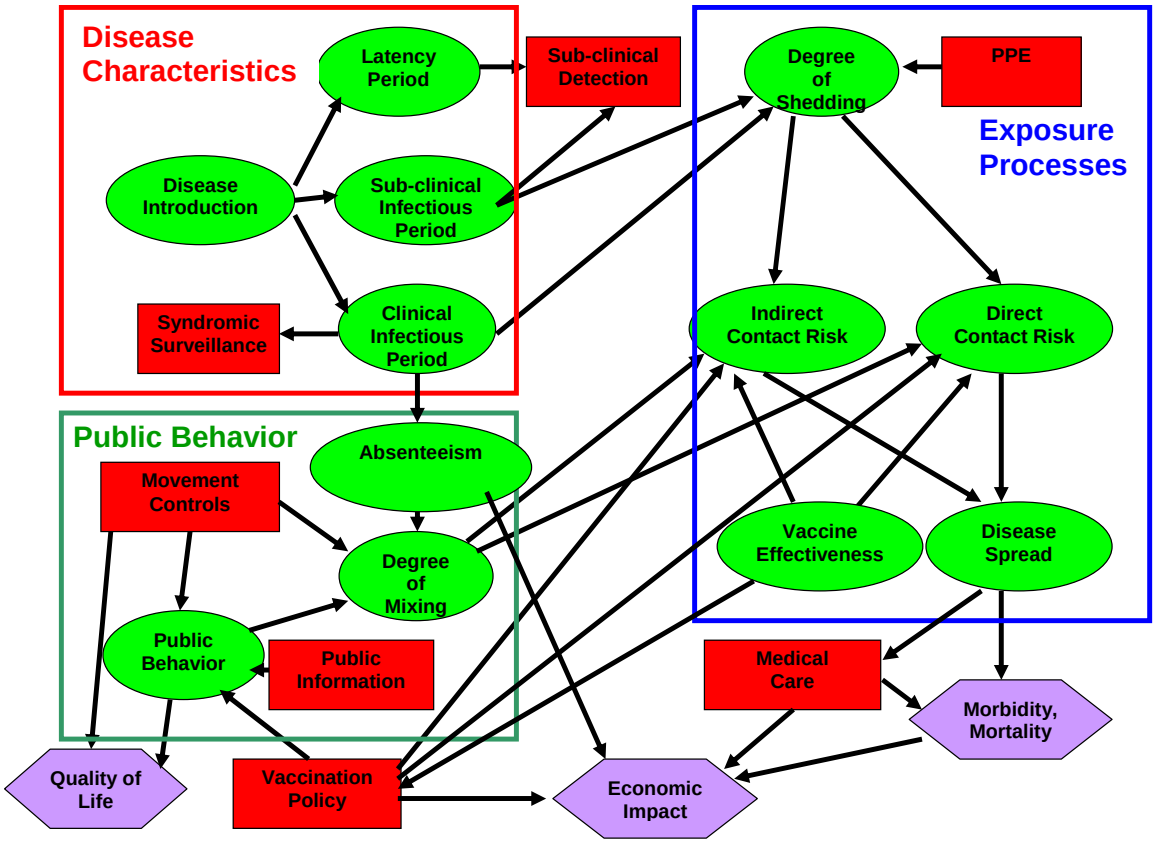


Figure 1: Influence diagram of variables and relationships affecting contagious disease spread during a major epidemic. These variables serve as a basis from which an effective nationwide human epidemiological model could be developed.

Variables in **Figure 1** were summarized into three high order groupings.[3] These included *disease characteristics*, *exposure processes*, and *public behavior*. *Disease characteristics* include important disease specific chance variables such as the latency period, the subclinical infectious period, symptoms of the disease, and the clinical infectious period. Disease symptoms that present and the clinical period affect *public behavior* since severe symptoms over a long duration are likely to lead to increased levels of work and school absenteeism. Absenteeism, in turn, affects the degree of mixing occurring during an

[3] Certain decision variables are largely driven by official responses to an outbreak and were not explicitly captured in these higher order groupings including medical care decisions, vaccination policies, and some detection systems.

outbreak, which is also influenced by public behavior driven by public information, vaccination policies, and movement controls. Infectious disease parameters influence *exposure processes* by affecting the degree of shedding that would take place from an infected individual. The degree of mixing also influences *exposure processes* by either increasing or decreasing indirect or direct contact risk.[4] Both the degree of shedding and the contact risks interact to ultimately affect disease spread, which will ultimately affect the amount of morbidity and mortality.

Figure 1 accounts for most of the decisions that public health officials need to make prior to or during an outbreak to attempt to contain the outbreak and as a result, the influence diagram is an end-to-end representation of a potential outbreak scenario. For example, vaccination policies and public information can be implemented either before an outbreak occurs or during an outbreak and in either case these policies would have a significant impact on public behavior and eventual disease spread. Similarly, policies regarding subclinical detection and syndromic surveillance must be implemented before an outbreak occurs although their true effectiveness would only be ascertained while the outbreak was occurring.

An effective model should account for all these variables in its implementation. An effective model would have the capability to assess preventative measures implemented before an outbreak occurs as well as responsive measures implemented after an outbreak occurs. An effective model would also incorporate a wide range of

[4] In this context direct contact risk refers to the physical relocation of an infected individual from an infected location to an uninfected location (e.g., a sick business traveler flying on an airplane). Indirect contact risk refers to the short-term (i.e., several hours) temporary relocation and mixing of individuals some of which might come from infected locations and some of which might come from uninfected locations.

control measures including prophylactic prevention, surveillance and detection tools, responsive resources, and behavioral controls.

After comparing the influence diagram to the literature review, we concluded that only two existing nationwide epidemiological models offer capabilities that capture most variables identified in the influence diagram: MESA and EpiCast. However, both models lack *public behavior*-related variables. In particular the explicit incorporation of variable compliance and a range of different behaviors (both good and bad) among affected populations appear to be missing. This is an area of future development and is discussed in more detail later in the document. Since the influence diagram confirmed that MESA incorporates most of the variables in the influence diagram we concluded that MESA would be capable of effectively simulating a large-scale human disease outbreak. The remainder of this document focuses on the application of MESA to a human disease.

3.1 Overview

MESA was initially developed as a generalized epidemiological model incorporating multiple geographic scales. It has the capability to model a parameterized infectious disease across a well-defined population and to evaluate the efficacy of countermeasures against that disease. A nationwide outbreak of influenza was chosen as a test-case for the model because empirical influenza disease data exists [MILLS 04; POTTER 01]. Alternative diseases such as smallpox, SARS, and plague were considered. However, influenza was the only disease out of these four alternatives that has routine occurrences throughout the country. The Centers for Disease Control and Prevention (CDC) continuously monitors influenza outbreaks and documents empirical data on each year's strain and prevalence [CDC 08]. Although influenza is generally a milder disease

than smallpox, SARS, or plague, recent concern regarding the potential for an H5N1 avian influenza pandemic in human populations has increased concern regarding influenza and the ability to model and predict the likely impacts from a major influenza outbreak [CDC 07].

Because MESA is a general epidemiological model, many of the components within the model are easily adaptable to various diseases, populations, geographies, and/or control measures. MESA parameters (initially set to model FMD spread through animal farms) were mapped to comparable parameters in human epidemiology (see **Table 1**). Each row in the table corresponds to a set of parameters within the MESA model that require specification for human epidemiology.

Table 1: Mapping between animal specified parameters in MESA and human specified parameters in MESA

MESA Generalized Parameters	Animal Specification	Human Specification
Entity populations	All animal farms in nation	All census tracts in nation
Entity types	Herd types (Dairy, Beef, Swine)	Human demographics (School-age, Workers, Elderly)
Intra-entity spread	FMD spread within herd	Influenza spread within census tract
Inter-entity spread	Indirect high risk, indirect low risk, direct local	Household spread, school spread, work spread
Long-range inter-entity spread	Sales yard animal movement	Airport human movement
Disease detection	FMD detection/confirmation	Influenza detection/confirmation
Control measures	Fast FMD-related controls	Slow Influenza-related controls
Movement controls	Stop animal movements	School/work closures

The MESA specification was broken down into five parts:

1) The underlying population,

2) Intra-census tract spread,

3) Inter-census tract spread,

4) Detection, and

5) Control measures.

The specific approaches used to define each of these functions within the epidemiological model are discussed in more detail below. It should be emphasized that the goal of this study was to demonstrate proof of concept on a disease with influenza parameters. The specification of several of these functions could be expanded upon or improved in future work, but for the purposes of this study the parameters were set to be demonstrative.

3.2 Population Model

The basic entity of the MESA animal disease model was the farm, which might consist of multiple animal herds of different types. Each herd had a given number of animals within it that are all of the same type. Herds were aggregated up to the farm level, farms were aggregated to the county level, counties were aggregated to the state level, and states were aggregated to the national level. In the MESA animal model it was recognized that FMD would spread differently in different herds because of varying disease spread parameters in different animal types and because the behavior of large herds might be different than the behavior of smaller herds. Therefore herd types were distinguished based on the type of animal in the herd and the size of the herds, which enabled herd specific input parameters to be set.

A similar structure was applied to human populations at risk of influenza exposure. Influenza will spread differently across different demographic groups in a similar way to how FMD spreads differently in different herd types. For example, school-aged children have different behaviors than elderly populations which could put them at a higher (or lower) risk of contracting a disease. Control measures implemented during a

real outbreak are likely to affect specific demographics differently (e.g., school, work, or airport closures, mandated vaccinations for certain demographics). Therefore different demographics in human populations were comparable to different herd types in the animal model. There are hundreds of different demographic variables distinguishing at-risk populations. To bound the problem, we focused on age-related demographics where behaviors are significantly different between groups.

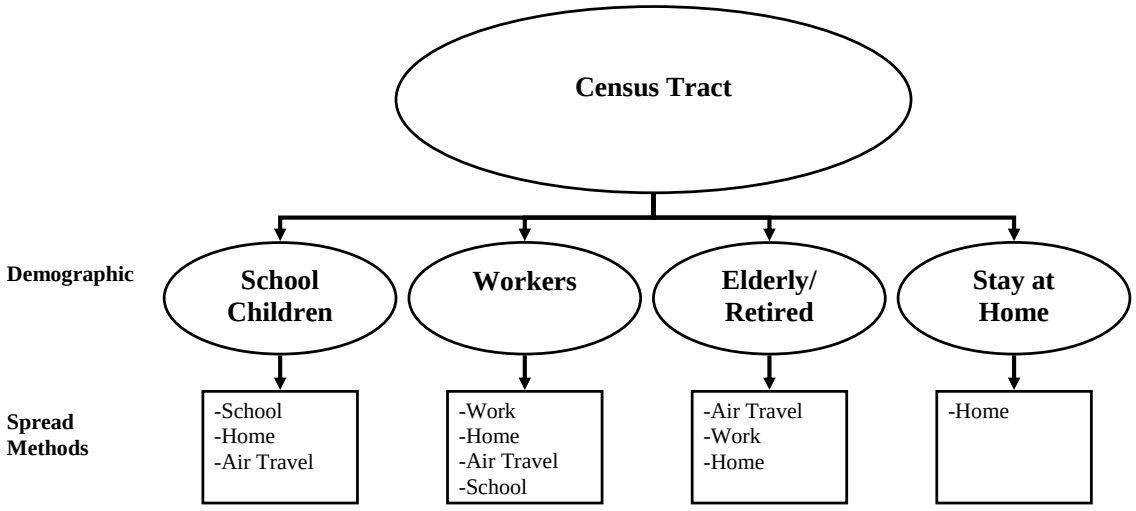


Figure 2: Breakdown of census tracts into four demographic variables and associated spread methods used for modeling human populations and disease spread using the MESA model.

The population was broken down into four over-arching demographics based upon their respective behaviors (see **Figure 2**):

- People between the ages of 5 and 20 attend schools during the day located near their home with an average enrollment rate of 75% [US CENSUS BUREAU 07]

- People between the ages of 21 and 61 attend work during the day with an average of 65% in the labor force [US CENSUS BUREAU 06b][5]
- People over the age of 62 are retired [GENDELL 01] and participate in community activities or staying at home during the day
- People less than the age of 5 and all others who do not fall in the categories above stay at home (e.g., pre-kindergarten children and stay-at-home parents)

There are over 65,000 census tracts across the country. The 2000 U.S. Census provides data on the demographics of each census tract [US CENSUS BUREAU 00]. In order to develop a human population model for MESA, 2000 U.S. Census data was collected for every census tract in the contiguous 48 states and the District of Columbia. Each tract's population was broken down into the four demographic groups identified above. This resulted in roughly 260,000 demographic groups representing about 304,000,000 people modeled in the human system, compared to 1,200,000 herds representing about 160,000,000 animals in the animal system [MELIUS 06].

3.3 Spread Models

MESA incorporates two different types of spread sub-models. An inter-census tract spread model is an agent-based simulation that enables spread from one census tract demographic to another. An intra-census tract spread model is an SEIR model and enables spread within a census tract demographic [SMITH 07]. These are synonymous with the inter-facility and intra-facility spread models in the animal model. Release

[5] The definition of 'labor force' adopted here includes those who are employed and those who are unemployed but actively looking for work. For the purposes of this assessment unemployed persons actively looking for work were treated in the same manner as those who are employed since unemployed persons looking for work would be interviewing at potential employers or traveling a great deal.

events are specified within the model to begin the disease spread process. In the baseline influenza scenario the index case was a school-aged child located in Queens, New York. In this section the assumptions used to populate each of the spread models for a baseline influenza scenario are described in detail.

3.3.1 Intra-Census Tract model

The intra-census tract spread model contains various disease parameters that enable disease spread between individuals within a specific census tract and demographic group. Each simulated day (i.e., a time step in the model) the model evaluated the number of susceptible, latent, sub-clinical infectious, clinical infectious, clinical non-infectious, and recovered individuals within the census tract. The number of subclinical contacts was specified for each demographic group and an SEIR model represented by a system of difference equations using the Reed-Frost method [ABBY 1952] used those contact rates to determine if an infectious individual spreads disease during a given time step. The implementation of the intra-census tract model is described in greater detail in [SMITH 07]. The model determined the fraction of individuals within a census tract demographic that fall into various disease states and the process iterated on the subsequent simulated day. The parameters adopted in the intra-census tract model for influenza are shown in **Table 2** and were the same parameters used in a comparable EpiCast influenza scenario [NIGMS 08].

Table 2: Influenza disease parameters assumed for baseline scenario

Disease Parameter	Value (days)
Latent State Duration	1.2
Subclinical State Duration	0.5
Clinical Infectious State Duration	3.5
Clinical Non-infectious State Duration	0

For a baseline scenario the values shown in **Table 2** were fixed, although in reality durations vary by individual. MESA has the capability to instantiate these inputs using statistical distributions and sample values from each of these distributions. The baseline model assumed school children have 5 similar contacts per day within their own census tract on average, adults have 2 contacts per day on average, the elderly have 2 contacts per day on average, and stay at home individuals have 1 contact per day on average.[6]

3.3.2 Inter-Census Tract model

The inter-census tract spread model simulated spread between infected census tract demographic groups and non-infected census tract demographic groups. The inter-census tract model within MESA consisted of several sub-models where each one simulated mixing between different census tract demographic groups. Each of these sub-models is referred to as a spread method. Spread methods may be one of two major forms, including standard spread methods and interstate spread methods. Standard spread methods only resulted in spread occurring between two census tracts that are located relatively close together, although they do not necessarily have to be neighboring. Interstate spread methods only resulted in spread occurring between two census tracts located far from one another. For purposes of illustration the baseline scenario implemented four different spread methods, three of which were standard spread methods and one of which was an interstate spread method. These are each described in greater detail below.

[6] These contact rates assumed contact between similar individuals living with or very near a given individual. The contact rates did not include school, work, home, or travel related contacts with people outside of the census tract.

School Spread

Disease spread through schools was one standard method for disease spread that integrated into the baseline model. Each class of students consisted of 30 students and each student comes into contact with two workers on average. Roughly each school in the United States is populated by students coming from two different census tracts, so it is plausible that disease would spread from a student in one infected census tract to another student originating from a neighboring uninfected census tract [NCES 07]. Average travel distance to a school for a typical student was five kilometers. These inputs were used by the school spread method to develop the average number of contacts between census tracts and demographics within a school.

Work Spread

Disease spread through work was another standard method integrated into MESA. We assumed a typical worker has 15 worker related contacts. The average travel distance to work was assumed to be 35 kilometers [US CENSUS BUREAU 06a], which enabled several workers from multiple census tracts to mix and raised the prospects that an uninfected census tract will become infected through the work spread method. The baseline scenario assumed that nearly all contacts at work occurred between workers, although there was a slight possibility that elderly (older workers who would otherwise be retired) could become infected from work-related disease spread.

Home Spread

Disease spread through the home was the third and final standard disease spread method incorporated into the inter-census tract spread model. Spread in the home was assumed to take place over an extremely small distance (~1 km) and enabled the

possibility of children, stay at home individuals, the elderly, and workers to interact and spread disease within a given census tract. The home spread method focused predominantly on spread between parents (i.e., workers) and school children. It was assumed that each household consisted of two adults and two children. There was also a small probability that elderly or stay at home individuals could become infected through this spread method since those individuals also mix with others in the home setting.

Interstate Spread

Interstate spread was incorporated through the integration of airport travel statistics. The Federal Aviation Administration (FAA) collects annual statistics on the number of passenger boardings occurring each year at all airports in the United States [FAA 06]. Airport boarding volumes for individual airports were aggregated up to the state level and an interaction matrix between states was built, assuming that the volume of air traveler boardings through any given state was directly proportional to the probability that any given traveler would fly to that given state. The 48 contiguous states were included in this interconnection matrix.[7] It was assumed that the 70% of airplane passengers were workers, followed by school age children (20%), followed by the elderly (10%).

3.4 Influenza Detection

For FMD and other rare, high impact diseases, detection of an occurrence is critical and warrants a major response. However, for the purposes of this study detection

[7] The District of Columbia was included in the matrix, although Reagan National Airport was included as a Virginia state airport, rather than a Washington DC airport. Once a passenger flies to a given state, a gravitational model places them into a given census tract based upon population density. Therefore, MESA's internal check ensures that high density areas, such as the Washington DC metropolitan area are more likely to become infected than rural areas.

played a less critical role since influenza outbreaks occur naturally and are normally not a major concern. For proof of concept, we assumed there was a 0.05 probability that a case of this disease presenting at a doctor's office would lead to a confirmation test and that this confirmation would result in a broader alert being issued across the infected county. The 0.05 probability value was chosen because there is likely to be a fair amount of misdiagnosis and victims might choose to self-medicate rather than seeing a doctor. The confirmation test delay was assumed to be three days and the alert delay was assumed to be two days.

The pandemic influenza outbreak of 1918 serves as an important reminder of the significance of correct and timely disease diagnosis. This outbreak was not immediately identified as influenza since symptoms were so severe that it was often misdiagnosed as a new infection or plague that caused pneumonia [BARRY 04; CROSBY 03]. Based on this historical example, there is a good chance that a severe outbreak of influenza could be undiagnosed for an extended period of time. However, for the purposes of developing a proof of concept model we assumed that run-of-the-mill localized influenza outbreaks with mild symptoms were distinguishable from a large nationwide influenza outbreak with more severe symptoms.

3.5 Control Measures

MESA has the capability to simulate a large number of different control measures at various points throughout the simulation. These include identifying infected premises, quarantining infected zones, designating disease surveillance zones, shutting down

interstate movements, responsive vaccination, and increasing disease awareness and surveillance.

To demonstrate proof of concept, simple social distancing control measures were modeled in the baseline influenza scenario. We assumed that one day after a suspected case was identified an infected premises would be declared across the affected census tract resulting in a reduction of school contacts by 30% and work contacts by 20% within that zone. Then one day after disease confirmation occurred an infected zone would be declared 10 kilometers around the infected census tract, reducing school contacts by 95% from their original values (i.e., essentially what might be expected from school closures) and work contacts by 80% from their original values within that zone. Also, one day after disease confirmation occurred a surveillance zone would be declared in the county where the infected census tract exists, reducing school and work contacts by 70% within that zone. A more draconian control measure was also implemented in the baseline model where air travel by infected people within a confirmed state would be shut down one day after an alert is issued. Although this may appear to be too restrictive during a realistic nationwide influenza outbreak, without this control measure, the disease propagated nationally before it was contained and often led to a worst-case scenario where the entire nation was infected.

4.0 Results

Using the baseline assumptions described above, 20 instances of the baseline scenario were simulated. MESA outputs statistics of the outbreak such as the timing of each spread event, the number of each affected census tract, the timing and types of countermeasures deployed, the overall duration of the outbreak, and the numbers

affected. Among the 20 simulated outbreaks, the average duration of an outbreak was 100 days (stdev = 53) and the average number of people affected was 52,000 (stdev = 49,000). Schools were the predominant spread mechanism and students were disproportionately affected by the outbreaks. On average, each outbreak spread to three different states, although this varied between one and six states. **Figure 3** plots the number of people affected by the duration (in days) of the outbreak for all 20 baseline scenario model runs.

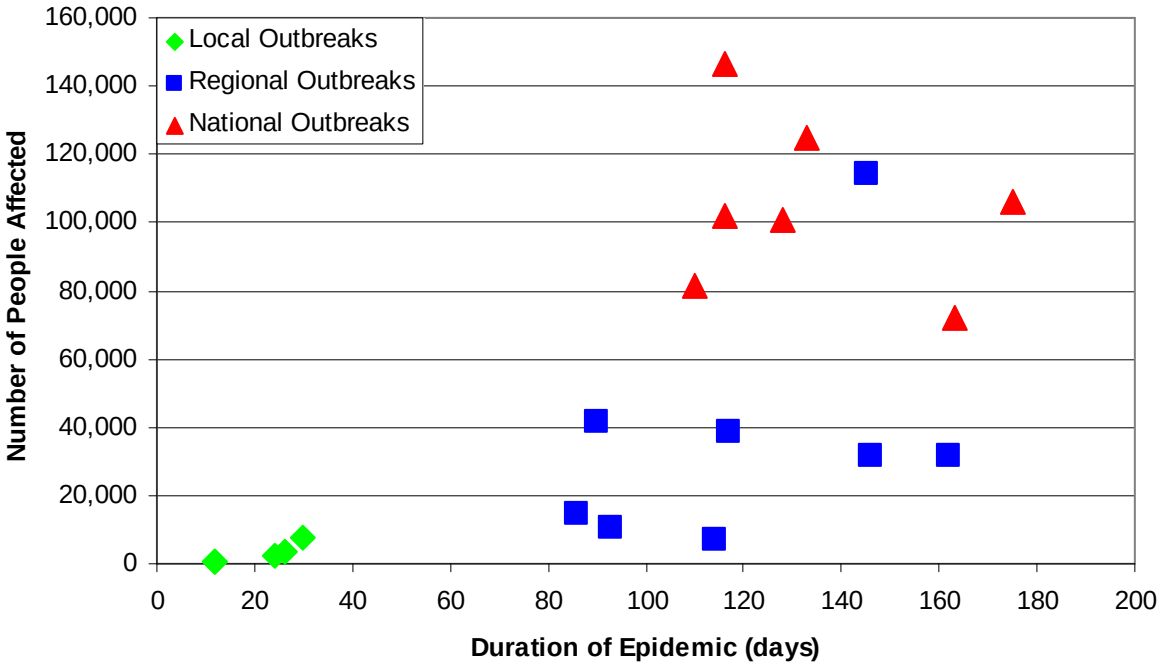
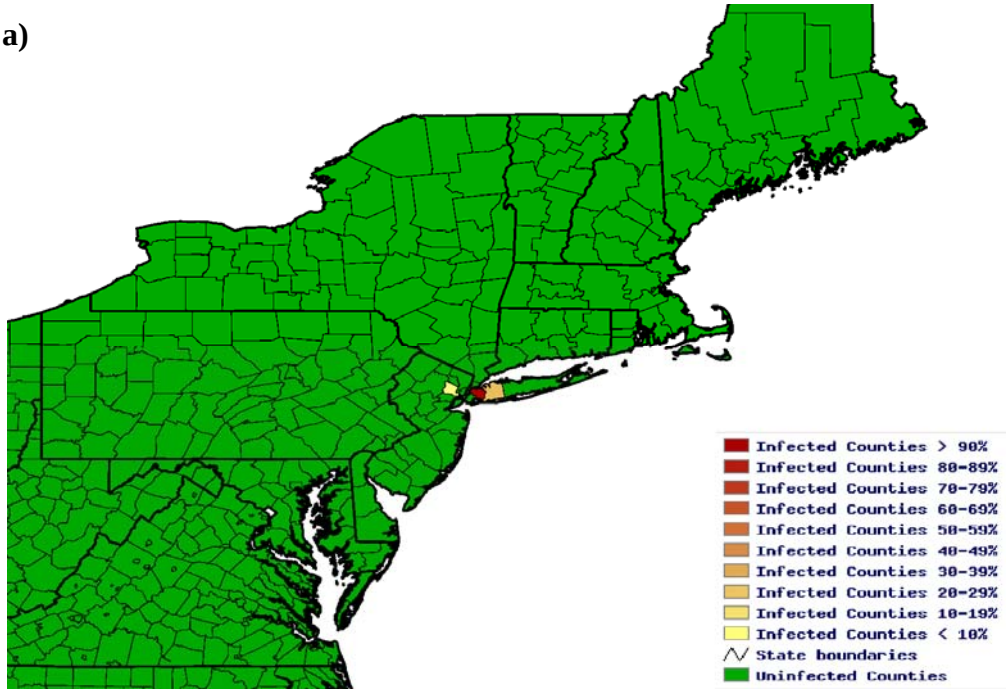


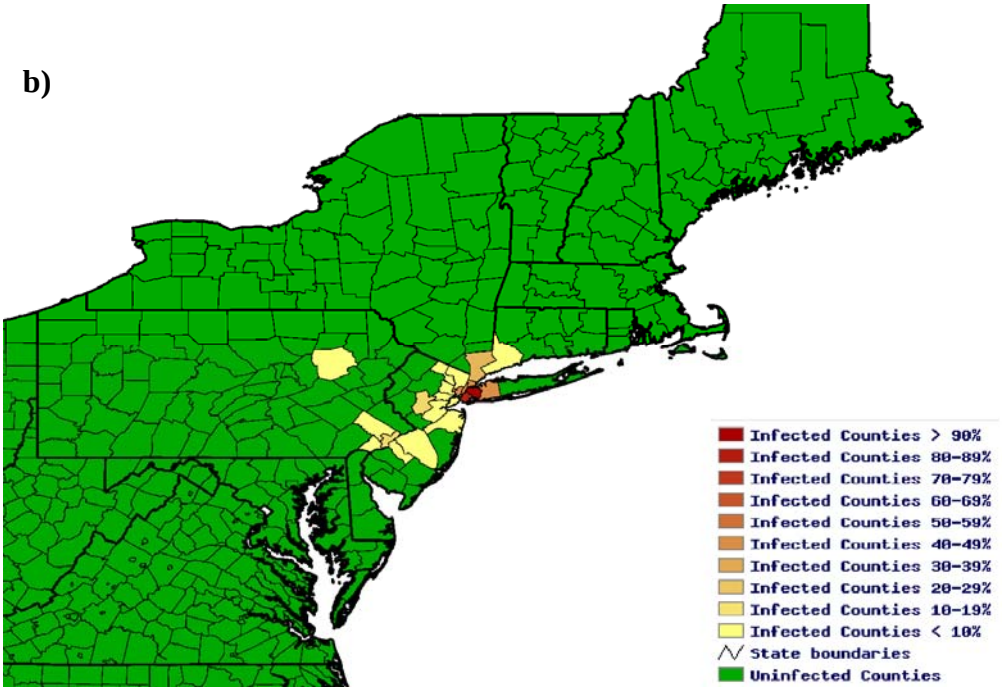
Figure 3: Number of people affected by the duration of the outbreak for all 20 baseline scenario model runs

Figure 3 shows that the simulated outbreaks could generally be classified into three types: 1) those that spread only locally (N = 5), 2) those that spread regionally (N = 8), and 3) those that spread nationally (N = 7). **Figure 4** illustrates the geographic extent of spread in each of the simulated outbreak types.

a)


Infected Counties > 90%
Infected Counties 80-89%
Infected Counties 70-79%
Infected Counties 60-69%
Infected Counties 50-59%
Infected Counties 40-49%
Infected Counties 30-39%
Infected Counties 20-29%
Infected Counties 10-19%
Infected Counties < 10%
State boundaries
Uninfected Counties

b)


Infected Counties > 90%
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Infected Counties 70-79%
Infected Counties 60-69%
Infected Counties 50-59%
Infected Counties 40-49%
Infected Counties 30-39%
Infected Counties 20-29%
Infected Counties 10-19%
Infected Counties < 10%
State boundaries
Uninfected Counties

c)

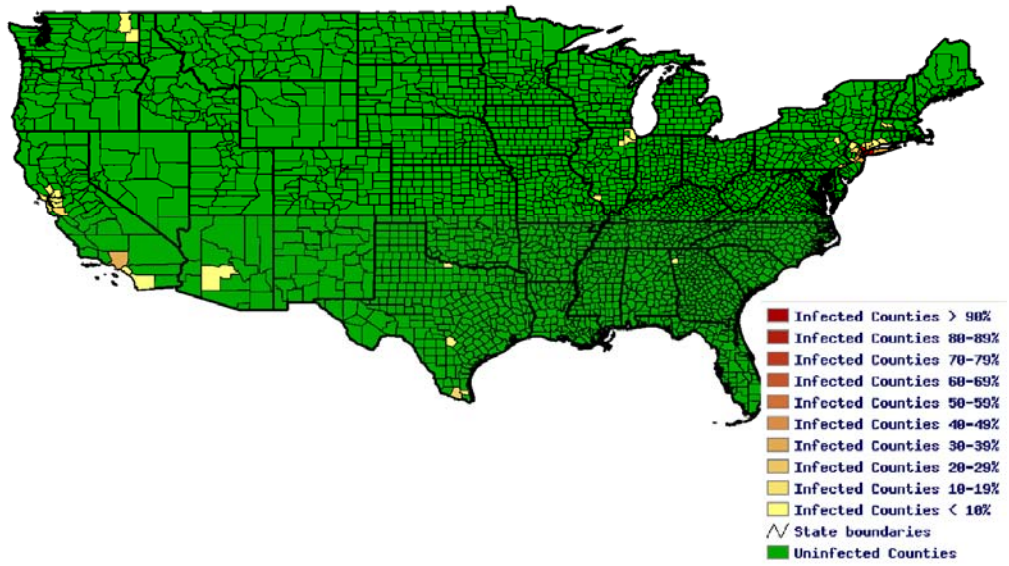

Figure 4: Geographic spread of each class of simulated outbreaks from the MESA model where a) is only local outbreaks, b) is only regional outbreaks, and c) is national outbreaks.

Among the local outbreaks, **Figure 4a** shows the disease generally burned out in the immediate area around its introduction in New York City. 83% of those infected in these outbreaks were school children and most of the spread occurred only in schools. These were outbreaks where the disease was not able to find new and unique hosts quickly enough or at sufficient distance before the disease was detected and stamped out or burned out on its own.

Among the regional outbreaks, **Figure 4b** shows the disease spread throughout the New York City Metropolitan Area and as far away as Philadelphia, but did not involve long distance travel. 49% of victims were school children and 40% were workers. These outbreaks were characterized by schools being hit the worst and workplaces being hit almost as bad.

Outbreaks shown in **Figure 4c** could be considered nation wide epidemics involving multiple states, with some states on different coasts of the country. These outbreaks also affected school children (45%) and workers (47%) almost equally. However, the distinguishing characteristic of these outbreaks was their ability to spread well beyond the point of introduction through at least one air travel event. While the disease was discovered and contained in the New York City area, it had an opportunity to spread without being detected or contained to distant locations (i.e., silent spread), which ultimately led to multiple regional outbreaks across the country until all instances were detected and contained.

Table 3 shows the average prevalence of spread methods and victims by demographic for each outbreak type.

Table 3: Average prevalence for each spread method and victim demographic by outbreak type

		Outbreak Type		
		Local Outbreaks	**Regional Outbreaks**	**National Outbreaks**
Spread Method	**Interstate**	0	0	3
	Home	30	37	31
	School	63	41	38
	Work	7	22	28
Victim Demographic	**School children**	83	49	45
	Workers	17	40	47
	Retired/Elderly	0	3	3
	Stay at home	0	8	5

Table 3 suggests that the role of workers increased in larger epidemics. This result makes sense since the model assumed that workers might travel long distances to get to work (relative to distances school children would travel to school) and workers were the most likely demographic to fly long distances. The retired/elderly and stay at

home individuals did not play a major role in any of the outbreaks, although they played a greater role in regional and national outbreaks than they did in local outbreaks.

These results illustrate the importance of incorporating and modeling long-distance disease spread through air travel. Even though empirical outbreak research identifies air travel playing a role in major outbreaks [VIBOUD 04], this analysis confirms and quantifies that effect. Considering the volume of daily air traffic over the United States on a typical day, the risk of a regional epidemic becoming a nationwide pandemic through air transportation is high. A nationwide spread model incorporating air travel as well as local spread behavior is needed to assess the potential of a nationwide pandemic and results shown here illustrate large impacts, even if some draconian countermeasures are implemented.

These results also show a high degree of variability for one fixed set of input parameters. **Figure 3** shows that even when input parameters are fixed, there is a great deal of variability that can occur between different instances of the model, due to natural variation in disease spread contacts, detection, and control measures. This result makes sense, since the events that distinguish a major outbreak from a minor outbreak are likely to be a series of worst-case random realizations of an underlying stochastic process. If a good understanding can be built of these underlying processes and the combination of events that lead to a worst-case outcome, then effective countermeasures (such as restricting air travel from infected regions) could be tailored to the problem. A next step in the analysis should be to perform sensitivity analysis with respect to:

1) Contact rates,
2) Disease parameters,

3) Detection parameters, and

4) Control measures.

5.0 Conclusions and Future Work

The model described in this paper is an incremental step forward in the modeling of human infectious diseases. Because of computational efficiencies, the MESA model runs quickly and incorporates natural variability in model output, which enables a broad range of stochastic analyses of output and explicit handling of uncertainty. The model offers an alternative to existing large-scale models since it enables the entire distribution of effects to be modeled and examined, whereas most other models are point estimate input/output models. Analyses of output from large-scale stochastic simulation models should account for natural variability in the process from run to run and the sensitivity of input parameters to those results [LAW 00].

Because of natural variability in the size and duration of outbreaks in diseases such as influenza and the probabilistic nature of disease spread at a local level, these outbreaks should be modeled stochastically so that the entire distribution of output for a given set of input can be examined. Although the output from point estimate models may be easier to visualize, explain, and understand than the output from a set of model runs, a set of model runs from a stochastic simulation presents the full and complete picture of potential impacts [LAW 00]. Predicting the course of a nationwide outbreak is particularly difficult since such an outbreak involves so many variables that are uncertain and variable in nature. The massive number of different spread mechanisms and their interdependencies requires a modeling methodology that can account for them and output that can capture the full distribution of variability that will inevitably occur.

The model described here has been used as a proof of concept to illustrate these issues and offer potential improvements to nationwide human epidemiological modeling. In real influenza outbreaks that have occurred in the United States over the past 30 years, most have been limited to regional or local small outbreaks. However occasionally (over a much longer time horizon) an outbreak grows to be out of control and becomes a national problem as the outbreak may have a tendency to spread faster than control measures are capable of monitoring and containing it [CDC 08; VIBOUD 04; POTTER 01]. Population movements and climate have been identified as major factors that influence the size and duration of influenza epidemics [VIBOUD 04]. Results from this study confirmed and quantified the population movement effect and this finding warrants further exploration to validate the model and its predictive capabilities. An epidemiological model should have the capability to incorporate variables that could distinguish a typical influenza year from the 1918 influenza pandemic and it should capture the variability that could lead to any sized outbreak between these extremes [POTTER 01; CROSBY 03].

Applying the MESA model to human epidemiology also illustrated that simply scaling up a regional small-scale model is unlikely to account for all the complex variables and their interactions involved in a nationwide outbreak. A census tract in rural Kansas is very different from a census tract in New York City. Different compositions of different demographics leads to different spread potential in these two census tracts and the behavior of individuals and local response efforts are likely to be different as well. A nationwide model should have the capability to capture and model these differences. Furthermore, the results from this study have shown the need for incorporating long-

distance spread through air travel between census tracts located far from each other. Scaling up a regional model and slapping a long-distance spread method on top of it would fail to differentiate specific airport volumes. Therefore we conclude that nationwide spread models are inherently different than local or regional spread models and future efforts to develop a nationwide spread model should require a new model, rather than scaling up existing regional models.

Despite these advantages of the MESA methodology described here, there are several limitations of the methodology and areas of improvement that should be explored in future work. These are discussed in greater detail throughout the remainder of this section.

5.1 Reliable Empirical Outbreak Data are Limited

Correctly characterizing the proper frequency of different sized outbreaks is critical to model development and validation against a particular disease. Unfortunately there are limitations in this area, since empirical outbreak data is often incomplete or unreliable for model validation. The CDC collects statistics each year on influenza cases and the prevalence of different strains of influenza in the general population [CDC 08]. However, the CDC data is limited. The data within each year's report presents national trends in the strain and outbreaks without providing enough detail regarding the disease spread characteristics to perform a useful validation study of the spread methods integrated into this model or other nationwide models. Therefore, the data can be used to assess the overall frequency of outbreaks and their general size. However, a more

detailed validation study would require much more specific disease spread data across specific demographics.

In order to address this limitation, epidemiological modelers should work with HHS to identify the characteristics of historical disease outbreaks that should be monitored in order to assist in model development and validation to improve existing epidemiological models. This has the prospect to change the way information is gathered regarding the disease and its spread. A better understanding of the information needed by the modeling community would help CDC focus its information gathering efforts. The dialogue between CDC and the modeling community is crucial for the modelers as well since they will become more aware of the limitations in getting reliable historical disease outbreak data for their models.

In addition to validating the model against reliable historical outbreak datasets, the model could also be validated against existing nationwide epidemiological models and its output, such as EpiCast. A similar baseline scenario could be run in both models and the output could be compared to identify differences in predictions. Model parameters and functions could be compared to identify potential advantages and disadvantages of each approach and where improvements could be made. Although one specific model is unlikely to represent truth, a suite of different independent approaches may better represent possible scenarios. By understanding the differences between these approaches and their output, a better understanding of their usefulness and applicability to practical problems will result, which could motivate the improvement of all models being used.

5.2 Expanding Spread Methods and Improving Disease Parameters

To illustrate proof of concept the model described here only implemented four spread methods across four different demographic variables. Although we believe these are four of the most crucial spread methods to include in a nationwide epidemiological model, there are many opportunities to expand the methodology into many other spread methods that could contribute to disease spread. **Table 4** shows various additional spread methods that might be implemented into a more comprehensive epidemiological model.

Table 4: Various spread methods that could be incorporated into the MESA human epidemiological model during future work activities

Spread Method	How method spreads	Demographic	Similar groups
Day-care	Indirect, 8hrs, 5 days per week	Child	Schools
Playgroups	Indirect, 2hrs, 5 days per week	Child	
Colleges	Direct/Indirect, duration	Adult	
Hospitals	Direct, duration	All	
Short-mid travel	Direct (vacation), Indirect (business)	All	Interstate
Hotels	Direct (vacation), Indirect (business)	All	
Churches	Indirect, 2hrs, 1 day per week	All	X
Community activities	Indirect, 2hrs, 1-3 days per week	All	X
Shopping	Indirect, 2hrs, 2-3 days per week	All	X
Gyms	Indirect, 1hr, 2-3 days per week	Adult	X
Parks & Rec.	Indirect, 2hrs, 1 day per week	All	X
Special Events	Indirect, 4hrs, 1 time	All	

Table 4 shows 12 different spread methods that could easily be integrated into the MESA epidemiological model. The inclusion of some or all of these methods would improve the realism of the model, although we believe the marginal contribution of each additional spread method to the overall model output is uncertain and could be relatively

small compared to the school, work, household, and interstate spread methods currently implemented. The table also shows how the spread method might be implemented in the model, specific demographics that the method would affect, and similar groups that would be implemented in a similar fashion. For example, since church, community activities, shopping, exercise at gyms, and visiting parks are sporadic weekend activities, they could be implemented in a similar fashion to one another or aggregated into a broader spread method class of weekend activities.

Other components of the model which may require further examination and expansion are the disease spread parameters and contact rates in different spread methods. Although better historical disease data could help to inform some of these parameters, discussions with experts in each particular disease spread method would build understanding of the parameters and develop more realistic contact rates between different groups for various activities. These experts would also be beneficial to examine model output and identify potential problems or unusual results that might require further examination and assessment.

It might be impossible to fully validate any large-scale epidemiological model without a large amount of empirical data to validate against. However, the inclusion of additional spread methods and validation through expert discussions would improve the underlying model and its results. Experts could examine the model and its output to determine if the results are consistent with what is known about the disease and whether or not the distribution of output correctly captures the distribution of historical outbreak data or what one would expect from a disease (if there are no historical datasets). Future work should prioritize model parameters for a more thorough validation study. A

systematic approach should be used to identify discussion points with experts and focus their attention on specific mechanisms within the model and its implementation. In discussions with experts, consensus should be reached on the values of parameters where possible and if it cannot be reached then those areas should be highlighted as areas requiring further study and exploration. Using this approach uncertainty in the values of critical parameters can be minimized and future research efforts to improve the fidelity of these parameters can be prioritized. In addition, sensitivity analyses could be conducted across the range of uncertainty specified by experts to better understand the range of impact that an uncertain parameter can have on an epidemic.

5.3 Incorporating Realistic Behavior

As mentioned earlier in the explanation of the influence diagram (shown in **Figure 1**) existing epidemiological models do a relatively poor job of incorporating realistic human behavior. For example, the MESA modeling methodology incorporates controls that shut down certain mixing behaviors such as school systems or work patterns, but it does not reroute entities to other activities, such as simulating hospital surge or disease spread within a hospital as it fills up with infected patients and worried well.

Existing modeling capabilities could be expanded to incorporate realistic behaviors that people are likely to express during a major epidemic. For example, during a real epidemic a public official might order specific at-risk groups to receive vaccinations which could limit the spread of the disease. There could be high degrees of non-compliance with this order if people do not trust authorities or if the message is

poorly delivered. Alternatively, there could be a large number of no-risk groups showing up to receive vaccinations if they suspect that they are at risk too. A more realistic model should have the capability to incorporate these varying behaviors. During the 1918 influenza pandemic hospitals became unsafe as the surge of infected patients overwhelmed hospital staff and many staff members became sick themselves. In response, doctors began making house calls, donning masks, and taking other protective actions against further disease spread [BARRY 05]. Models might need to incorporate certain dynamic behaviors and triggers such as these to expand the range of countermeasure architectures that might be developed on the fly during a real outbreak. Models might also need to account for certain specific locations that will become concentrated areas of disease spread such as convalescent homes, hospitals, and clinics where infected patients might congregate.

These changes might require significant revisions to nationwide spread models. Before conducting such an expansion effort, critical variables should be identified that would have a major impact on model outputs. Attention should be focused on those variables when models are revised. If an exploratory sensitivity study concludes that some behavioral variables will not have a major impact or that existing parameters in the models could account for variations in behavior, then a full model expansion effort could be avoided. If a full model expansion effort is warranted, then it should focus on expanding those areas that deviate most from reality and would have the most significant impact on an outbreak.

5.4 Countermeasure Architecture Studies

The model limitations described above have been focused upon validation-related issues. Once a validated model is attained, there are a number of studies that could be conducted with the model to expand our knowledge base of disease spread and control mechanisms. The baseline model described here implemented only a small subset of countermeasures for demonstrative purposes. However, since MESA is an end-to-end modeling capability, it has the ability to integrate any number of various countermeasure strategies that could be triggered at different times in an outbreak. Therefore, countermeasure architecture studies could be conducted to evaluate the potential of different intervention strategies on an existing disease and its spread.

It would be useful to better understand which countermeasures show the greatest potential with realistic assumptions of countermeasure efficacies and under current resource constraints. For example, in the case of influenza it would be useful to know how effective a responsive vaccination policy would be using current knowledge on the effectiveness of the vaccine on major disease strains and the size of the vaccine stockpile. The effectiveness of a responsive vaccination policy could be compared to the efficacy of social controls that could be ordered across vulnerable populations, such as closing schools and limiting contacts between at-risk individuals. Similarly, detection assumptions should be examined in sensitivity studies since they could play a major role in identifying the outbreak and distinguishing a major epidemic from small-scale outbreaks. Once overall countermeasure efficacies against a particular threat are better understood then more detailed policy analyses could be conducted to understand which countermeasure policies hold the most promise at containing disease spread. These

studies will inform policymaking decisions such as the size of national stockpiles, the placement and distributions of those stockpiles, personal protective equipment (PPE) required at care centers to limit disease spread, and resources required to minimize social control delays.

It would be useful to evaluate these decisions for known threats, such as influenza. However, large-scale modeling capabilities also enable an assessment of rare or unknown threats, such as biological attack agents (e.g., smallpox) or rare natural diseases such as SARS. Although validating such an epidemiological model would be extremely difficult to do because of a paucity of empirical data, the insights developed from countermeasure architecture modeling studies against these threats would be useful to guide high level policymaking and make general recommendations for managing emerging threats.

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ACKNOWLEDGEMENTS

This work has been completed as part of an Engineering Techbase project and a Laboratory Directed Research and Development (LDRD) Feasibility Study within the Engineering and Global Security Directorates at LLNL. The authors would like to thank Daniel Faissol for his contributions to the literature review. The authors would also like to thank Doug Speck and Dale Slone for MESA modeling technical support. The authors extend special appreciation to Annette MacIntyre, Bill Hanley, Rob Sharpe, and David Rakestraw for their support, guidance, and assistance with this project. This work was performed under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under Contract DE-AC52-07NA27344.

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