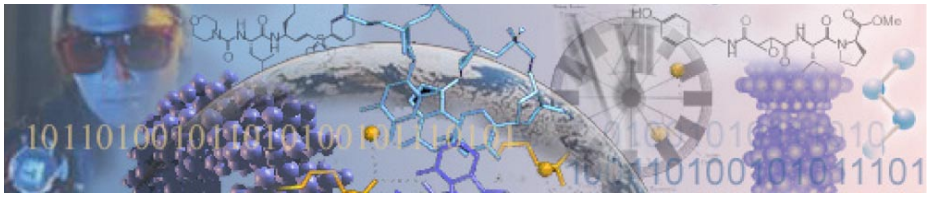

Science and Technology Expert Partnership

Mathematical Modeling of the Spread of Selected Bioterrorism Agents —*Summary of an Open Conference*

Scientific & Technical Intelligence Committee
National Intelligence Council

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An Introductory Note

In the current international climate, there is considerable concern regarding bioterrorism, with attention directed toward the dispersion and spread of bioterrorism agents by a variety of mechanisms.

To address this and many other areas of concern to the national security, the STEP (Science & Technology Expert Partnership) program was developed as a National Intelligence Council (NIC) and Scientific & Technical Intelligence Committee (STIC) initiative to bring together government and national experts. This STEP activity was suggested by Dr. Lawrence Gershwin, National Intelligence Officer for Science and Technology, and was overseen by Dr. James Kvach, Chief Scientist of the Armed Forces Medical Intelligence Center (AFMIC) of the Defense Intelligence Agency (DIA). DIA/AFMIC is a member of the Intelligence Community (IC) and a crucial element of the Department of Defense's (DoD) force protection planning. In addition, Dr. Ellis McKenzie of the NIH and Dr. Alfred Steinberg of MITRE collaborated in inviting speakers, finalizing the program, and in co-chairing the conference. In order to focus the meeting, only a few bioterrorism agents were considered. It is anticipated that future conferences will address additional bioterrorism agents, including animal and plant pathogens.

This report was prepared by Alfred D. Steinberg, M.D., The MITRE Corporation, for the Scientific & Technical Intelligence Committee. Comments and queries are welcome and may be directed to Dr. James Kvach, Chief Scientist, Armed Forces Medical Intelligence Center (301) 619-7511.

Mathematical Modeling of the Spread of Selected Bioterrorism Agents— *Summary of an Open Conference*

Summary

Models clarify thinking, provide a mechanism for asking important questions, and assist policy-makers in their decision-making and crisis management. One important aspect of model development is to identify the few critical parameters that have the greatest effect on the outcome. Values for these parameters (herein called "drivers") need to be refined. This is an iterative process in which the models should become progressively more useful as additional data become available, important parameters are refined, and dispersion/spread models become more sophisticated.

Mathematical modeling of the spread of bioterrorism agents is a developing field. Although considerable effort has been expended to create relevant models, much more research and development work is required. Many of the variables needed for models are still not well-understood. Some of these may not even be well-approximated in some current models.

Microbial agents which spread person-to person, such as the smallpox virus, can give rise to an epidemic, whereas agents that affect only those individuals who are initially exposed, such as anthrax spores, cannot. For agents that are contagious, the number of secondary individuals that each initially infected person subsequently infects (termed the Ro) is of critical importance in predicting the rapidity and breadth of the spread of an outbreak, and the public health measures needed to contain it.

From the models presented at this conference, it is clear that a single release of anthrax spores, which do not spread person-to-person, can cause large numbers of fatalities but not a national or international epidemic. An attack with an agent that is passed person-to-person, such as smallpox, can potentially cause a nation-wide epidemic and possibly even a world-wide crisis, requiring early detection, vaccination, and quarantine if it is to be controlled.

Short Statement of the Problem

In order for the US Intelligence Community (IC) and the policymakers it serves, to be better prepared to deal with national or international acts of terrorism, we need to understand the role that mathematical modeling of the spread and/or dispersion of bioterrorism agents might play in crisis management and public health decision-making. The purpose of this

conference was to determine the baseline ability of mathematical modeling to forecast the local, national, or international spread of an infectious disease due to an act of bioterrorism.

Findings and Forecasts

General:

1. Mathematical modeling can be an important tool to: sharpen understanding of fundamental processes, compare alternative policies and interventions, help to make decisions, provide a guide for training exercises and scenario development, assist risk assessment, aid forensic analysis, and predict future trends.
2. Decision-oriented models can be of great help in preparing for, and responding to, bioterrorism events much as they are in business, engineering, war, and other fields.
3. Models are tools to assist —not replace—critical thinking and to help in deciding which questions are most important.
4. There is inadequate support in the U.S. for the development and testing of mathematical and computational models for forecasting the spread of infectious diseases.
5. Mathematical modeling of the spread of infectious diseases has not yet become a mature discipline.
6. Several models have been developed that describe aspects of the spread and/or dispersion of microorganisms that could be used by terrorists. These models can provide useful information to policymakers and crisis managers.
7. Few policy-level consumers of bioterrorism models are well-informed about models, modelers, or the modeling process.
8. Modeling for each microorganism requires values/assumptions for that agent as well as other factors, including details of initial release and population at risk.
9. Agents which can be readily passed person-to-person have the greatest potential for national or international spread.
10. There are insufficient data to support various aspects of mathematical modeling research and development.
11. Identifying the few critical parameters (no more than 3-5) is an important aspect of model development.
12. Future work should include refinement of the values for these critical parameters.
13. The basic reproductive ratio (Ro), which describes the potential for a communicable disease to spread, is a critical parameter and should be estimated for all contagious human and animal diseases with bioterrorist potential. A Ro >1

allows an infectious disease to spread in a population, whereas an Ro<1 is associated with diseases that die out.

14. No two epidemics are identical. A Ro from a prior disease outbreak may not accurately describe a new event with a similar organism.

Findings for Smallpox

1. Smallpox is a contagious disease with the potential for causing a world-wide pandemic.
2. Smallpox spreads as a result of person-to-person exposure, resulting in secondary and tertiary cases (in contrast to anthrax, which is not passed that way).
3. A high Ro for smallpox (the number of individuals an infected individual will in turn infect) would predict much faster spread with greater likelihood of a difficult-to-control epidemic than for a lower Ro.
4. There is disagreement regarding the proper Ro for smallpox models.
5. Some smallpox models assume uniform mixing of the population whereas others assume that infected individuals will expose specific contacts with whom they have had "face-to-face" interactions during their contagious period. This difference is important in predicting outcome and in directing public health measures.
6. There is disagreement regarding the value of vaccinating contacts of infected individuals versus vaccination of the general population. Models that incorporate uniform mixing suggest mass vaccination whereas models that stress infection of contacts suggest vaccination of contacts for control.
7. Smallpox models suggest that delaying vaccination programs is very undesirable because there is a significant increase in casualties for each day of delay.
8. Quarantine reduces fatalities and helps to bring an epidemic under control in the models in which it was examined.
9. Quarantine and vaccination for smallpox outbreak control are superior to employing only one or the other.

Findings for Anthrax

1. Inhalation anthrax can occur after spores are inhaled, but infection is not passed person-to-person.

2. Although inhalation of 8,000 spores is considered to be the LD50 for anthrax in humans, the anthrax dose-response curve is broad, suggesting that the LD5 or LD10 might be substantially less. Indeed, two models predicted that between 5%

and 10% of individuals exposed to somewhat less than 200 spores would die from anthrax.

3. The number of casualties after an anthrax release could be markedly reduced if evidence of the anthrax release is determined immediately.
4. For an agent with a relatively high infectious dose such as anthrax, meteorological conditions may be a critical parameter in determining the number of casualties.

Findings for Plague and Tularemia

1. The microorganisms that cause plague and tularemia are more susceptible to atmospheric decay than are anthrax spores.
2. For an agent with a low infectious doses, such as tularemia, unstable meteorological conditions can lead to wider spread of the agent and worse consequences.
3. For both tularemia and plague, evidence of a release prior to clinical and laboratory diagnosis is critical to preventing large numbers of fatalities.
4. Quarantine would assist in reducing secondary spread of pneumonic plague.

Findings for Foot and Mouth Disease (FMD)

An epidemic was simulated for a portion of California based upon conditions believed to exist currently for USDA-mandated diagnosis and control of FMD.

The result suggested that much faster diagnostic techniques could play a critical role in disease control.

Pre-emptive ring slaughter was estimated to be more costly and less effective than pre-emptive slaughter of only the highest risk herds surrounding an infected herd.

Mathematical Modeling of the Spread of Selected Bioterrorism Agents— *Summary of an Open Conference*

Purpose

The purpose of the Conference was to determine the baseline capability of mathematical modeling to predict the spread of pathogenic microorganisms used as bioterrorism agents.

Background

Mathematical modeling has the potential to assist in government planning for, and crisis management of, bioterrorism events. Indeed, modeling is well-suited to understanding what is known about the dispersion and/or spread of pathogenic microorganisms used as bioterrorism agents and to highlighting areas where additional information or work is needed.

This conference was arranged by The MITRE Corporation for the STIC as part of the STEP program. This is the third in a series of scientific programs to advance state-of-the-art knowledge. The first was held in September 2000, and the topic was mathematical modeling of infectious diseases. The second, held in September 2001, was on the future capabilities of genomics and proteomics by the year 2012.

The first of these modeling conferences concluded the following:

The field of modeling of the spread of various infectious diseases or forecasting conditions suitable for infectious disease outbreaks is still in its scientific infancy.

Modeling standards must be established.

Modeling of infectious disease epidemiology should be multidisciplinary, and include infectious disease experts, immunologists, modelers, statisticians, and epidemiologists.

Such modeling requires good data or superb assumptions, which must be easily testable.

If more than one group models a disease, resolving the bases for differences may allow the field to move forward. Without such resolution, users of modeling information may develop a lack of confidence in all models and their results.

Combining relevant portions of two different models may provide synergy.

It may be desirable for non-linear systems to be used as "expert systems" by non-modeler users to avoid an excess of parameters.

There is a great difference between diseases that are transmissible from one human to another and those in which the human is a "dead end" host. The modeling of these is very different in the details of the parameters used.

The best models allow reasonable conclusions that could be utilized by non-modelers, for example, epidemiologists and policy makers.

It is relatively easy to generate models, but validating them is a problem. Making the models predictive is especially difficult.

Models can be iterative, and predictive models, even when incomplete, are useful.

Models are able to tell what is known, the relative importance of different factors and, where we do not know enough, which information may foster improvement of the models.

This second conference on modeling of infectious diseases brought together experts in the areas of mathematical modeling of selected bioterrorism agents, including the causative organisms of anthrax, smallpox, plague, and foot and mouth disease. The experts were associated with government, academia, and industry. The conference included healthy debate and provided insights into the strengths and limitations of different approaches to mathematical modeling of the spread of infectious diseases.

Introductory Presentations

Dr. Alfred Steinberg, *The MITRE Corporation*

Mathematical modeling can provide information, estimates and predictions useful to policy-makers. Models also can provide new insights. An example is found in a report on modeling of bubonic plague (Nature 407: 903-906, 2000.). For years, experts had trouble understanding why quarantine and rat control measures did little to prevent the occurrence of plague within a city. The model in the referenced Nature paper shows that *Yersinia pestis* may persist in a rodent population from which occasional human epidemics can arise without the need for external imports. Plague reservoirs in wild rodent populations serve as sources of infection for urban rodents. Moreover, when the urban rat population falls, plague-infected fleas jump from former rat hosts to humans, thereby leading to excess cases of plague. This model helps to explain why plague recurred after long disease-free periods, and how the disease could arise despite strict quarantine controls.

In this meeting, we hope to determine what is known about modeling of the dispersion and/or spread of certain biological agents, and which refinements might occur with additional work. Our emphasis is on a few selected bioterrorism agents so as to focus our efforts. We believe that whenever possible, it is useful to indicate the degree of uncertainty around assumptions and the resulting uncertainty of predictions. If a model finds that prions in England's sheep can yield between 15 deaths and 150,000 deaths from variant Jacob-Creuzfeld disease, that result is not too helpful for planners. However, such a result could point to critical variables that, when better studied, might narrow the range of predicted casualties.

Dr. James Kvach, Chief Scientist, *Armed Forces Medical Intelligence Center (AFMIC)*
Expectations of the Conference

Dr. Kvach stated that this conference intends to focus on modeling the spread of human diseases caused by biological warfare (BW) or bioterrorism agents, but that a future conference should emphasize the spread of diseases caused by plant and animal pathogens. He reminded the audience of our September 2000 conference on mathematical modeling of infectious diseases. This first conference revealed the lack of, but the absolute need for, multidisciplinary modeling teams that, at a minimum, should include infectious disease experts, immunologists, modelers, statisticians, and epidemiologists. Based upon the first conference, he has secured two-year funding for modeling work on the spread of bubonic and pneumonic plague. He anticipates that by the year 2005 it will be possible to develop a model able to predict conditions suitable for outbreaks of Rift Valley fever in Africa.

Dr. Kvach indicated the need for a study on the interrelationship between behavior and infectious diseases. In addition, the development of a pathogen genome database and global genomic surveillance will enable significant advances in molecular epidemiology which in the future will provide valuable data and aid infectious disease modelers.

Dr. Ellis McKenzie, *Fogarty Center, NIH*
Introduction

Dr. McKenzie noted that there is little support in the U.S. for the development and testing of mathematical and computational models of natural occurrences of infectious diseases. A broader range of disciplines is often required for modeling bioterrorism events. More experts are needed, but the relevant expertise takes time to develop. Quality control in modeling derives from regular interactions and peer review among modelers, but the appropriate networks have not been established. Few policy-level consumers of bioterrorism models are well-informed about models, modelers or the modeling process. If end-users and model-makers can communicate clearly and often, decision-oriented models can be of great help in preparing for, and responding to, bioterrorism events much as they are in business, engineering, war and many other fields. Indeed, this conference provides an unusual but valuable mechanism for bringing together a major group of experts working on these problems.

Session I. Chairperson, Dr. Ellis McKenzie

Dr. Fred Roberts, *Rutgers University*
Overview. Why Models?

Dr. Roberts gave an introductory lecture on modeling. He pointed out that there are many kinds of models: maps, scale models, computer models and mathematical models.

Mathematical models make use of the most precise language invented by humans. The use of such language enables us to reason and analyze. These models are widely used by government and industry. Even if a model is a failure, enough may be learned by the process to justify the effort expended. Models developed for one field may be useful for other fields as well.

Modeling and bioterrorism.

1. Components of host-pathogen systems are numerous and their interactions complex. Intuition alone is usually insufficient to fully understand the dynamics of such interactions.
2. Experiments/field trials are often too expensive, unethical or not possible.
3. Often there is insufficient data to make informed decisions.
4. Mathematical modeling becomes an important tool to:
   a. sharpen our understanding of fundamental processes
   b. compare alternative policies and interventions
   c. help make decisions
   d. provide a guide for training exercises and scenario development
   e. guide risk assessment
   f. aid forensic analysis
   g. predict future trends.

5. Because there may be no closed solutions to these problems it may be necessary to run computer simulations.

Mathematical models are widely used to formalize problems, refine questions, determine need for additional data, determine need for changes in assumptions, provide choices among policies, etc.

Simplified models are useful for formulating ideas, thinking about relevant factors and forcing us to define terms and goals precisely.

Dr. Peter Merkle, *Defense Threat Reduction Agency (DTRA)*
Overview. Why Biological Models?

Dr. Merkle paid tribute to: (1) Dr. Akira Okubo (1924-1996), a pioneer in biological modeling, (2) Dr. Horst Agerty, who treated U.S. military personnel for smallpox in 1946, and who assisted in a 1999-2000 DTRA smallpox modeling study, and (3) Dr. John Bombardt, a participant in this conference, for vaccine strategy modeling.

Dr. Merkle pointed out that various disciplines with overlapping domains are brought to bear in modeling the dispersion and spread of biological agents. These disciplines include: medical and biological sciences, environmental engineering and aerobiology, physical and environmental sciences, atmospheric sciences, mathematics, military operations research, political and military arts and sciences, defensive military medicine, military operations research and weaponization studies.

Biological Warfare (BW) modeling includes preparations and responses. The modeler must consider both natural outbreaks and deliberately enhanced outbreaks. So-called natural agents may be known causes of common or rare diseases, emerging or re-emerging diseases, organisms resistant to standard drug therapy.

A serious and unusual outbreak may not be a BW event. The "natural" outbreak of cryptosporidium in Milwaukee in 1993 rendered ill more than 400,000 people.

The basic reproductive ratio (Ro) describes the potential for a communicable disease to spread, but no two epidemics are identical. A Ro from a prior event may not accurately describe a new event with a similar organism.

Why models?
1. Model preparation can help to assess response options and inform decision-makers.
2. Modeling can assist in determining the impact of vaccination program delays on an event (e.g. smallpox models suggest that delaying vaccination programs is very undesirable; there is a significant level of additional casualties for each day of delay).

Dr. Merkle pointed out that it is too easy to develop a model that lacks suitable predictive capability. And great care must be employed in model building. Models as complex as technically possible may remain operationally useless.

Dr. Merkle suggested that in the future, a research project could employ volunteer human populations wearing biological detection devices and GPS systems. This system could

provide data to calibrate models for spatial movements and interactions of individuals, critically necessary to understanding human to human transmission.

Dr. Charles Penn, ***Center for Applied Microbiology & Research (CAMR), Porton Down, UK***
Smallpox and Plague Models – A UK View

Dr. Penn presented a short history of CAMR and its role in providing advice to government with regard to microbial risk assessment, diagnosis, and countermeasures. For example, in the event of an influenza pandemic, it might be necessary to close schools or public places, curtail travel, etc.

The microbial risk assessment (threat assessment, risk assessment, planning and response, risk communication) includes responses to deliberate release of an agent, such as anthrax, smallpox, plague, botulinum toxin.

Dr. Penn described three components for modeling bioterrorism risks:

1. Initial release (dispersion, initial casualties)
2. Potential epidemic spread
3. Management and control (policy)
   A. Stochastic and deterministic models (epidemic, public health preparedness and controls)
   B. Monte Carlo simulation techniques (variability and uncertainty)
   C. Sensitivity and scenario analysis

Dr. Penn discussed the difference between viewing a population as being characterized by individual cells in which contact occurs with adjacent cells, versus viewing a population as having homogeneous mixing.

Smallpox is viewed as especially serious because it is infectious by the aerosol route and is infectious person-to-person. As a result, there is the potential for epidemic spread. Indeed, a serious outbreak of smallpox in Great Britain could give rise to 40 million cases/50 million population and a total of 12 million deaths if no attempts were made to control the epidemic.

Suggested countermeasures include:

1. Rapid detection
2. Mobilization of resources
3. Quarantine of cases (and the "security" of such quarantine/isolation)

4. Contact tracing
5. Vaccination and quarantine of contacts

An important factor is the number of cases that have to occur before the outbreak is detected.

Dr. Penn presented a model used to predict the effects of control options on the kinetics of disease. Unfortunately, for many parameters, there is uncertainty.

If smallpox were to strike the UK, tens of millions of people might be affected within 3 months without intervention. The longer the delay in diagnosis of the first cases, the greater the number of individuals ultimately affected (Gani R and Leach S. in Nature, 13 December, 2001, and a correction in the February 28, 2002 issue).

Dr. Penn felt that the most important output of the model was getting a handle on the few critical parameters. For example, early diagnosis and contact tracing requires far less vaccination to stem the epidemic.

Dr. Penn pointed out that plague has a shorter latent period (4.2 days) than smallpox (7-17 days) but also a lower transmission rate (Ro) person-to-person.

Dr. Penn emphasized that it was difficult to get good data on values to put into the models. It is useful to incorporate such information as land use, demographics, movement of people. However, even if the same model were run a second time, one might get somewhat different results.

Discussion:
There was some disagreement regarding the Ro for pneumonic plague. Dr. Bombardt (IDA) suggested that it might be possible to have an Ro for plague as high as 4.

Dr. Castillo-Chavez (Cornell) agreed that movement of people could be a critical factor. In Argentina, 30% of tuberculosis cases could be traced to riding long hours on public transportation (buses mainly).

Questions:
What if smallpox is released in several different places in the UK? *Answer*: That would make the problem much more difficult.

What if several different bioterrorism agents were released? *Answer*: That has not yet been modeled.

Dr. Houston Dewey, *CIA*
Modeling the Smallpox Threat – Implications.

Dr. Dewey suggested that stochastic models suffered from a need to perform many Monte Carlo runs. He presented a "simple" deterministic SEIR model using STELLA to show the effects of quarantine and post-exposure vaccination.

This model can simulate a smallpox epidemic caused by purposeful release of the virus in the U.S., help us to understand the effectiveness of interventions, and assist in the rapid assessment of alternative strategies. The model assumes complete, homogeneous mixing of a population.

The number of initial cases is the "seed." The greater the seed, the faster the epidemic progresses and the earlier interventions must be initiated to control the epidemic. Thus, early recognition becomes imperative.

Dr. Dewey also presented the case of a smallpox variant with shortened incubation time, increased lethality, and lack of susceptibility to standard vaccination. This variant would kill many people early and would lead to many deaths. If infectivity was held constant while the other assumptions were allowed, there would be a rapid onset of disease and it would burn out.

Comments:
The assumption of homogeneous mixing is a problem. The opposite of homogeneous mixing – vaccinating contacts and quarantine – is a current public health policy in both the U.S. and the UK. This is discussed at the end of the report in the "Discussion" section.

Session II. Chairperson, Dr. Alfred Steinberg

Dr. Lawrence Gershwin, ***National Intelligence Officer for Science and Technology***

Dr. Lawrence Gershwin, National Intelligence Officer for Science and Technology, made a short presentation in which he indicated the need for information from mathematical modeling of the dispersion/spread of biological agents of concern. What are the key parameters? How confident are we of the assigned values? What additional data are needed? What are the key uncertainties? Dr. Gershwin emphasized the need for quality control over the models, and for those using the models to be better aware of the work of colleagues. He also indicated a need for a similar conference on plant and animal pathogens.

Ms. Julia Burr, ***Institute for Defense Analysis (IDA)***
Medical Countermeasures: The Case for Rapid Prophylaxis

Ms. Burr discussed casualty assessment, medical effects, and points for intervention. The approach she presented was to determine the expected time-phased casualty onset for three bacterial diseases: anthrax, plague and tularemia. For this work, she used NATO Allied Medical Publication 8, *"Estimation of NBC Battle Casualties, Volume 2: Biological*. She also examined the use of nine different delivery systems (explosive munitions, sprayers), eleven operational scenarios, and optimal weather for dissemination. She next examined the impact of initiating post-exposure prophylaxis based upon various triggering events and the effect of time required to implement prophylaxis.

Ms. Burr's assumptions were the following:

1. The biological agents would be of a quality similar to those of the defunct U.S. offensive program.
2. All exposures would be via aerosol.
3. Antibiotics would be 100% effective when used as prophylaxis.
4. Antibiotics are effective within a few hours of the initial dose.
5. Compliance rates would be 100%.

For anthrax, tularemia, and plague, peak casualties occur on day 4 after an attack, and most casualties occur by day 6. However, the time of laboratory diagnosis is several days after the onset of symptoms. Thus, without strategic warning of such an attack or detection of an attack with some collection/analysis system, it would not be possible to utilize prophylactic antibiotics in time to have a major benefit.

Therefore, Ms. Burr next discussed medical surveillance triggers. Her work suggests that there currently are insufficient data to evaluate. The 2% casualty rate, a datum that might trigger medical intervention, does not occur until day 3. Her results show that detection of an attack on day 0 would prevent all casualties. Detection with medical surveillance (day 3) would prevent 71% of casualties, but laboratory diagnosis would prevent only 12% of casualties. A lag of only one day in recognition of a prior attack by medical surveillance would lead to only 29% casualties avoided (*vs.* 71% avoided) and a lag of 2 days in medical surveillance would lead to only 12% of casualties avoided. Thus, rapid diagnosis is critical to preventing casualties.

Ms. Burr concluded that post-exposure prophylaxis can reduce casualties from battlefield attacks with anthrax, plague, and tularemia. The earlier the prophylaxis is initiated, the greater the benefit. Even a one day lag will largely negate the potential benefit of prophylaxis.

Dr. Richard Babarsky, *National Ground Intelligence Center (NGIC)*
Hazard Prediction/Consequence Assessment

Dr. Babarsky discussed issues in the modeling of transport and diffusion of airborne agents of mass destruction. He uses CATS-JACE, a GIS/CAD-based hazard prediction/consequence assessment tool. CATS includes a broad spectrum of hazard prediction and consequence assessment models integrated with hundreds of GIS databases. JACE is web-based with client-server applications. It includes adaptation for three-dimensional buildings and building response/agent release models.

Such transport and diffusion models typically generate an ensemble averaged concentration field which does not produce a realization of the random variable. However, the probabilistic output may provide a sense of the range of realizations. Such models generate averaged concentrations of agent which depend on changes over time. These models require a turbulence model, on which diffusion algorithms are based, and meteorological data to feed the flow algorithm. The latter data may range from a single fixed wind vector to high resolution forecasted data fields.

If one is studying release of a given mass at a particular point in time and space, a Gaussian plume model with Lagrange mathematics is useful, especially for short ranges. Such Lagrangian models avoid artificial diffusion associated with point source and Eulerian advection schemes. However, such a model would not be as good for representing longer range BW effects.

Some of the variables that might affect agent dispersion are wind, precipitation, decay, and urban effects. Urban effects are of interest to the government. Within cities, there are apparent wind anomalies, agent entrapment, and channeling effects. Buildings become vertical boundaries. Current methodologies represent paramaterized dispersion around buildings, and there is a requirement for enormous amounts of data for operational use. Studying urban effects requires building three-dimensional models of urban centers using various software. Bioagent properties include density, median effective dose at a breathing rate of 15 L/min, median particle size and size distribution, daytime decay rate, nighttime decay rate and agent purity. One can also couple models of dispersion within a building with the model of the initial release and propagation of agent in the exterior. An example presented showed the spread of anthrax spores within a building. Some rooms were skipped, apparently because of the air handling system.

Dr. Babarsky also presented hazard assessment of a scenario in which a cropduster (a USDA AGDISP model for agent droplets) was used to attack the crowd at a large racing car speedway in the Midwest.

Mr. Timothy J. Bauer, *NSWCDD, US Navy*
Hazard Assessment Model

A weaponized biological agent is one that has been processed for dissemination:

1. Dry: purified, dried, and milled (> 50% pure).
2. Slurry: organisms in an aqueous growth medium (2%-20% pure plus growth medium components)
3. Wet: toxins in an organic extraction solvent (>10% pure).

In addition, the weaponized agent may be encapsulated or mixed with additives to enhance survivability, but such treatment may affect particle size.

Particles < 10 microns in diameter are respirable and do not settle out quickly as do larger particles. For dispersion of a biological slurry from a sprayer, the droplet median diameter must be < 100 microns before a significant fraction of the resulting particles are small enough to be respirable.

All agents “decay” (become less viable) from exposure to the atmosphere. UV light from the sun is one of the important factors causing decay.

Toxicity calculations are based upon breathing 15 L/min.

For anthrax, using a median effective dose of 8,000 spores (an amount required to infect 50% of the people exposed), a dose of 182 spores was calculated at a probit slope of 1.0 for the dose required to infect 5% of the exposed people.[1]

Dr. James Koopman, *University of Michigan*
Transmission Modeling for Surveillance

Dr. Koopman presented a vision of a surveillance system with real-time web-based reporting. Hospitals, doctors' offices, volunteer families, and public institutions that record absences will all participate. Included will be sales of health-related items.

The NetSurv project of Biomedware, Inc. provides the software for this effort. The analysis system will provide a transmission model of infection transmission dynamics affecting agents spread by air, direct contact, food, water, needles, and insects. Updating will require a full-time team of three epidemiologists-modelers that serve public health districts of approximately 10 million people as well as a team of 10 such professionals at the national level.

It is envisioned that this system will be able to encompass different model types. Initially, there will be two compartmental models, one deterministic and one stochastic. There also will be two individual models: an individual event history model and a dynamic network model. The models will be altered as needed and as assumptions change. The output of the system will include evaluations as to the natural transmission dynamics as well as evaluation of possible modes of dissemination. Such reports could trigger more detailed evaluation and sample collection.

Dr. Koopman believes that controlling a new pandemic of influenza is like controlling a major bioterrorist dissemination of a transmissible agent. The conferees pointed out that there is no suitable vaccination strategy or therapy for some bioterrorist agents as there are for influenza. Moreover, influenza outbreaks can be anticipated from world-wide surveillance, whereas bioterrorist attacks cannot be anticipated in that manner.

[1] It should be noted that this not too far from the LD10 of 128 spores calculated by Dr. Houston Dewey as reported in this conference.

Drs. Tim Carpenter and Mark Thurmond, ***School of Veterinary Medicine, University of California, Davis***
Foot and Mouth Disease (FMD)

The presentation focused on a spatial-temporal, stochastic model with 40 parameters, 3 modes of transmission, and 12 herd types. An epidemic was simulated for a portion of California based upon conditions believed to exist currently for USDA-mandated diagnosis and control of FMD. The measures included slaughter of infected herds, quarantine, and restrictions on movement. The results suggested that much faster diagnostic techniques would have a great effect on disease control. Also helpful in limiting disease spread would be vaccination with the appropriate serotype vaccine (which might not be available in great enough quantity). Pre-emptive ring slaughter was estimated to be more costly and less effective than preemptive slaughter of only the highest risk herds surrounding an infected herd. Needed are effective biosecurity systems put in place by herd owners prior to an epidemic, enforcement of mandatory restrictions on movement of animals, vehicles, and personnel during an epidemic, and immediate slaughter of affected animals.

Dr. Carlos Castillo-Chavez, ***Cornell University***
Comments

Dr. Castillo-Chavez discussed issues involved in using viruses as agents of mass destruction. He also detailed some of the factors of epidemiological hosts:

1. a cell within a host
2. an individual who may pass the agent of disease to another individual
3. a vector (fleas in bubonic plague)
4. a cluster of individuals (coworkers, friends, family)
5. social landscape (who mixes with whom)
6. mass transportation (approximately 30% of tuberculosis cases in Argentina come from exposure in mass transportation systems)
7. house or building (may be the unit of infection)
8. cities, states, countries (global scope)

There are a number of mathematical approaches to such epidemiological issues:

1. Dynamic systems
2. Bio-economics
3. Simulations
4. Statistical modeling
5. Spatial models (lattice-based)

6. Agent-based models
7. Graph theory

If the Ro is <1, the disease dies out. If the Ro is >1, an epidemic is maintained.

Dr. Castillo-Chavez discussed terrorist groups (cells) as an epidemic process. He suggested that understanding such cells in this light might better equip the government to respond to the terrorists.

Session III. Chairperson, Dr. Ellis McKenzie

Ms. Monica Giovachino and Dr. Neil Carey, *CAN Corporation (CANC)*
An Epidemic Model of Plague

CANC is helping the District of Columbia Department of Health (DOH) with planning responses to bioterrorism events. CAN developed a model that simulates attacks using five different bioterrorism agents. The model includes the following: a case presents to the hospital, the hospital notifies DOH, DOH declares an emergency, diagnosis is confirmed, DOH locates the source of the outbreak, the DOH implements an intervention program. The model allows the DOH to examine the response times necessary to prevent deaths in a variety of scenarios.

The user of the model inputs the number of infected people and the time to start intervention. The output is the number of new cases and number of deaths each day.

The model contains assumptions for each disease based upon information in the medical literature. These can be changed by the user. The basic assumptions necessary to run the model for a plague outbreak are:

1. epidemic curve
2. fatality rate without intervention
3. success rate of intervention program
    a. symptomatic vs non-symptomatic
    b. time from exposure or symptom onset
    c. percentage of population receiving prophylaxis
    d. percentage of the population that is isolated
4. transmission rate
5. illness duration prior to death
6. capacity of intervention program
7. a fatality rate of 57% without intervention
8. success rate of 90% if intervention occurs prior to symptoms
9. a transmission rate of 1:2
10. infected people are contagious one day after onset of symptoms

The model was demonstrated for plague at three different levels of inhaled dose: 10,000 organisms, 1,000 organisms, and 10 organisms. Prophylaxis/intervention with antibiotics occurred on one of the following: day 2, day 4, day 6, day 8. Quarantine levels were 50%, 75%, 90%.

The results demonstrated that intervention by day 2 was the most important factor in reducing fatalities. Quarantine of at least 75% of people also was helpful.

Dr. Jonathan Davis, *Dynamics Technology, Inc., Arlington, VA*
Modeling the Spread of Bubonic and Pneumonic Plague

This effort combined the critical elements of plague epidemiology into a disease propagation model. It also investigated the effects of human behavior on disease spread. This would lead to an assessment of government and societal influences on plague transmission.

Multiple species are involved in plague spread: rodents, fleas humans. The sylvatic cycle between wild rodent and flea gives rise to bubonic plague when humans become involved. Urban rodent-flea cycles also occur. These also can cause bubonic plague. And a person with pulmonary involvement with plague can spread disease directly to another person (pneumonic plague).

The model is a multi-patch geographic generalization of Keeling and Gilligan, 2000. The essentials involve human-rodent-flea interactions, patch-patch ecological variation, travel and migrations, climatology, effects of vaccination, rodent control, resistance of rodents to *Y. pestis*, pesticide applications. Data still to be included are population densities, transportation information, vaccination rates, climate, prevalence, and immunity.

Future needs will also include surveillance coverage and rodent control strategies.

A simulation of plague spread though the patches of a 10x10 grid was presented. It was felt by Dr. Davis that this methodology might be applicable to a number of questions involving bioterrorism with plague as well as to other diseases, such as Rift Valley fever, tularemia, viral encephalitis, and smallpox.

Dr. John Heinbokel and Dr. Jeff Potash, *Center for Interdisciplinary Excellence in Systems Dynamics, LLP*
Plague

Dr. Heinbokel discussed a system dynamics approach to nonlinear modeling of human dynamics in bubonic and pneumonic plague. This method would make explicit different

mental models. It obliges individuals to be clear and precise regarding the mental models they use.

He discussed an SIR model. In the past, many models have dealt with Ro directly but not with the components that define Ro: contacts per unit time, infections per contact, the operational elements of the situation that are amenable to control by public health or other measures. The failure to include such items may lead to an overestimate of Ro.

The model he presented deals with a deployed military unit, but he stated that it can be generalized. He ran the model with changes in parameters: per cent of population initially exposed, contacts/hour, delay in diagnosis, treatment capacity. Since the military unit involves a working force, sick individuals who are removed or even contacts sent to the medical unit for therapy are unavailable to the force. In the worst cases, such a reduction was estimated to go from an initial force of 10,000 soldiers down to 2,000 soldiers.

Discussion:
The applicability of this model to civilian populations was questioned. Also, it was suggested that decision-makers tend to think in probabilistic terms rather than in deterministic, compartmental model terms.

Question:
There was a question about how fast the model could be run during an actual event. *Answer:* The time to run the model was much less than the time to acquire the data on the event and to react.

Dr. John Bombardt, *Institute for Defense Analysis (IDA)*
Smallpox

Dr. Bombardt wished to acquire actual epidemiological data sets for smallpox, plague, and Ebola outbreaks to assist in model building. On the basis of epidemiological data, he reconstructed historical outbreaks and made estimates of potential secondary infections for new initial conditions and modern outbreak controls. From the historical outbreak data, he developed an epidemic model using the Monte Carlo method and SEIRV difference equations for outbreak dynamics. He emphasized the smallpox work. Key epidemiological issues were: frequency of face-to-face (2 meter) contacts, "reach" of individuals via transportation systems, indoor versus outdoor encounters, customs, epidemic response time (diagnosis, initiation of controls), adherence to controls and therapies.

He found that smallpox has an average asymptomatic period of about 12 days, a 3 day prodrome (fever, malaise, enanthem), and a 7-14 day contagious period during the expression of rash (pustules, papules, vesicles, scab formation and scab separation).

Key events in the 1972 outbreak in Yugoslavia prior to 1972, the last case of smallpox in the country was in 1927. On 2/16/1972, symptoms began in the index case in Danjane. Between 3/1/1972 and 3/7/1972 onset of symptoms of 11 first generation cases. One of these first generation cases with hemorrhagic smallpox gave rise to 38 second generation cases, many of them hospital personnel. Together, there were 139 second generation cases and 24 third generation cases. Smallpox was first diagnosed on 3/14/72. A vaccination program was started on 3/16/72, one day after the initial second generation case became symptomatic, and it was continued until 4/30/72 at which time a total of 18 million people were vaccinated out of 20.8 million. He estimated the Ro (number infected per case) as 11, which is higher than other estimates at this conference. He felt that data from the modeling could be used for planning future responses should there be an outbreak in the military.

Dr. Martin Meltzer, *Centers for Disease Control and Prevention (CDC)*
Smallpox

Because smallpox is a potential weapon, it is important to determine the effectiveness of possible interventions, such as vaccination and quarantine.

Dr. Meltzer presented a Markov model with probability functions that the following groups/states of disease:

1. incubating
2. prodromal
3. overtly symptomatic
4. no longer infectious
5. the proportions of people moving from one to the next.

With an initial number of people infected set at 10 and a transmission value, Ro, of 1.5, a total number of cases was calculated as 224,000. If, however, the transmission rate was raised to 3, there would be billions of cases.

Using the number infected as 100 and an Ro = 3, and with a 25% quarantine rate and a 33% vaccination rate, the model gave a total number of cases of 4,240. If the Ro is increased to 5 and the other factors held constant, there would be 54,500,000 cases. If the Ro is

reduced to 2 but the quarantine rate is reduced to 10% and the vaccination rate is reduced to 25%, the total number of cases would be 10,512.

His conclusions were:

1. Based upon previous smallpox outbreaks, an Ro of 3 may be high
2. To control smallpox spread, one needs quarantine + vaccination
3. A stockpile of 40,000,000 doses of vaccine would be adequate for the U.S.
4. Who should be vaccinated is an issue because the vaccine does have side effects, although infrequent (about 1:100,000 to 1:500,000). The answer depends upon the estimate of the risk of release (something that cannot be known in advance).
5. If the risk of release is > 1:50, one could justify pre-exposure vaccination of personnel subject to the greatest likelihood of contact with an infected person
6. For the general population, post-exposure vaccination would be most efficacious in balancing risks and benefits
7. In modeling smallpox, it is most useful to first formulate the precise question and then to build a model to answer the question. In doing so, one will identify the critical "drivers."

Dr. Meltzer suggested that the major purpose in modeling should not be to narrow confidence intervals but to identify the few critical "drivers" (3-5 at most).

Dr. Greg Wilson, *Los Alamos National Laboratory (LANL)*
Modeling the Spread of Smallpox Using EpiSims

The problem addressed is how to respond to a smallpox attack in a city. Smallpox is detectable, has a long incubation period (7-17 days), is communicable, is lethal to many affected and is susceptible to vaccination.

Some of the options for biological agents are:

1. mass vaccination
2. mass quarantine
3. targeted quarantine + vaccination
   A. identify disease
   B. isolate affected
   C. vaccinate contacts

The goal of #3 is to detect the first wave of affected individuals, stop transmission in the second wave, and prevent the third wave. Effective early action will not only reduce the number of people affected but will inspire public confidence.

The EpiSims model involves a city, Portland Oregon, that has already been modeled based upon household surveys (carpool, work, lunch, home, shopping, bus, daycare, school, etc.) and other information. EpiSims complements traditional epidemiological models.

1. It uses traditional rate equations to model subpopulations
2. Subpopulations are based on a few demographics (<15 years, 15-55 years, >55 years) and exposed (E), susceptible (S), infected (I), recovered (R)
3. Subpopulation mixing rates are unknown
4. The reproductive number (Ro) is not measurable
5. Included are such factors as sub-location mixing, health-related activity changes, interventions
6. It accepts standard epidemiological assumptions regarding smallpox:
   A. An interaction with someone contagious with smallpox for 1 hour at 6 feet distance provides a 90% chance of contracting the disease.
   B. Lethality is 33%
   C. Smallpox is susceptible to vaccination (a 4 day head-start for the immune system is needed; better protection is afforded by prior vaccination)
   D. Detectability (a misdiagnosis is unlikely)
   E. Ring vaccination will stop the smallpox outbreak before the third wave. This requires:
      (i). sufficient vaccine
      (ii). contact tracing
      (iii). quarantine

Use of this knowledge model helps to define the structure of a complex problem so that quantitative analysis tools can be employed. It formalizes assumptions. It can quantify expert judgment for use in simulations. Outputs from the model were not presented.

Session IV. Chairperson, Dr. Alfred Steinberg

Dr. Jay Boris, *Naval Research Laboratory (NRL)*
Dispersion Prediction With Zero Delay and High Fidelity

Dr. Boris presented his 3-dimensional Containment Transport model called FAST3D-CT, developed at the U.S. Naval Research Laboratory. The model provides a detailed scenario generator with buildings, streets, paths, landscape features (including individual trees), etc. This model works on such platforms as SGI-O3K and Mac-G4. The model is used to generate a set of compressed data tables that encompass enough information to describe an exterior, ground-level, release scenario for any wind strength/direction with 85-90% accuracy of full 3-dimensional solutions.

A series of Gaussian similarity solutions and detailed simulations were compared for times after a point source of an agent was released in the landscape. People leaving the buildings were traced. Agent spread can be monitored from sensors located within the field of concern. If told to walk perpendicular to the path of the wind early in an attack, individuals could meaningfully reduce their exposure to agent. Some of this material is published in the March/April 2002 issue of Computing in Science and Engineering.

Drs. Fred Harper, John Brockmann, and Richard Griffith*, Sandia National Laboratories*
Dispersion of Anthrax and Tularemia

Dr. Harper presented work on modeling of aerosol dispersion, including movement within a building. Some of the factors considered include:

1. number of people outside at time of release/passage of plume
2. meteorology
3. building configuration
4. building operating conditions
5. agent source
   A. dissemination
   B. particle size and distribution (1-5 microns)
   C. mass
   D. decay in atmosphere
   E. infectious dose of 10,000 CFU for anthrax and 30 CFU for tularemia
   F. lethality of 0.99 for anthrax, 0.35 for tularemia
6. Agent transport

A. vapor and particle
B. deposition and adsorption
C. concentration
D. temperature

7. consequence model
   A. respiration -- 10 L/min
   B. population demographics (deaths, casualties)
   C. area contaminated/contamination level
   D. building operations modification

Several scenarios were modeled:

1. Wet release of anthrax and tularemia over New York City and Los Angeles
2. Dry anthrax release over New York City and Los Angeles
3. Anthrax release at a baseball world series game

Results: Release of 10 kg tularemia over lower Manhattan in New York City at a velocity of 10 m/s and a path of 1 km would lead to up to 1,622,000 people exposed and 175,000 fatalities (worst case) if 15% of people are outside and buildings provide a protection factor of 50 and there is maximum dissemination efficiency.. The same type of release over Los Angeles would lead to 1,374,000 exposed and 29,300 fatalities. An anthrax release over New York City would lead to up to 2,623,000 exposed and 438,000 fatalities. Such a release over LA would lead, in the worst case, to 3,688,000 exposed and 150,000 fatalities. The major factors in determining the number of fatalities were the meteorological factors (as much as 30X) and the original amounts of agent released. For an agent with a relatively high infectious dose, such as anthrax, stable meteorological conditions result in higher casualties. For an agent with a low infectious dose, such as tularemia, unstable meteorological conditions can lead to wider spread of agent and worse consequences. Biological decay can be an important factor (10X) for vegetative forms of bacteria.

In the baseball stadium scenario, heat from the spectators modified the results. For an anthrax release, up to 51,800 fatalities might occur. If the meteorological conditions are less stable, people in the surrounding area would be affected, leading to as many as 171,000 fatalities.

Modeling of effects within buildings utilized such factors as gravitational settling, turbulence, Brownian diffusion, wall roughness, air ducts – size, bends, etc. Also included is placement of an array of sensors that will assist in pinpointing release and in calculating concentrations as agent spreads through the building.

Dr. Houston Dewey, *CIA*
Dispersion of Anthrax

Dr. Dewey discussed the LD50 of anthrax versus CW agents. The CW agent VX has a very narrow dose response range with a sharp upswing, so that there is no illness until a threshold dose is reached, but a slightly higher dose is lethal for nearly 100% of individuals. Thus, the LD10 is very close to the LD90. In contrast, inhalation anthrax appears to have a very shallow upswing in its dose-response curve and a rather broad curve. Therefore, even if 8,000 spores represents the LD50 for inhalation anthrax, the LD10 may be much less and the LD90 may be much greater. Using an LD50 of 8,000 spores, it was estimated that the LD10 for anthrax was approximately 120 spores[2], and the LD90 more than 500,000 spores.

Anthrax particle size distribution also was addressed. A crop duster, with typical agricultural settings, sprays in such a manner as to prevent dispersion onto adjacent farms. The particle sizes will be large with only a small percentage in the respirable range. However, if someone fits a crop duster with a spray system that generates small particles in the respirable range, such a delivery system could cause serious problems. Moreover, small sized anthrax particles tend to act like a gas – they get into buildings. This is different from VX released outside which is mostly excluded from the interior of buildings.

There has been much written in the news about the particle sizes of the anthrax in letters to people in the U.S. – e.g. it was weaponized. It is useful to remember that such reporting did not provide data on offensive program anthrax size distributions or the anthrax letter size distribution. Also, it did not take into account that some of the letter material may have been squeezed out prior to analysis, and the material squeezed out may have been of small size.

Dr. James M. Wilson, *Infectious Diseases Working Group, Global Disaster Information Network*
Remotely Sensed Epidemic Intelligence (RESPI)

Dr. Wilson discussed remotely sensed indicators and warnings of epidemics of Venezuelan Equine Encephalitis (VEE), a potential bioterrorism agent which has been produced for BW purposes and weaponized.

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[2] This compares with an LD5 of 182 spores calculated by a different method by Mr. Bauer as presented at this meeting. Also, an LD7 for monkeys was approximately 300 spores when an LD44 was 5,000 spores (Bact. Rev. 30:657, 1966).

An epidemic of VEE occurred in 1995 in Venezuela and Columbia. It commenced in April at the beginning of the rainy season. Markedly increased remotely sensed NDVI values correlated temporally and spatially with the appearance of VEE in equine herds in east Falcon State. A precipitation surge in August to November, again was detected by NDVI, corresponded to the major rainy season, and correlated with the surge in human cases observed in Maracaibo, Venezuela, and expansion into La Guajira, Columbia in September.

In this example pilot study of RESPI, Dr. Wilson and his colleagues observed evidence for possible climatic modulation of the onset and propagation of VEE. Genomic sequencing suggested the possibility of accidental introduction of the virus by a local laboratory. Thus, it may be useful to monitor by remote sensing indicators of environmental conditions suitable to the spread of such vector-borne agents.

Future uses of RESPI include:

1. Epidemic initiation "forecasting": climate conditions favorable for VEE epidemic initiation.
2. Epidemic propagation "forecasting": spread once VEE is identified in sentinel equine populations.
3. Bioterrorism identification: (a) remote identification of conditions favorable to deployment of a given bioagent, (b) remote identification of conditions favorable for spread of such an agent far beyond its initial release point.

Dr. Ellis McKenzie, Fogarty Center, National Institute of Health (NIH) Comments

Dr. McKenzie noted that the meeting had been marked by its diversity of approaches as well as its overall excellence. Different numerical estimates in seemingly similar circumstances, as occurred in several cases, are very familiar in modeling, particularly in relatively new fields. Over time, common goals can be set, methods clarified, models verified and validated, and discrepancies resolved through networks of modelers and model consumers. One completely robust conclusion here, with respect to bioterrorism events, is that rapid, appropriate responses are critical, and that these require good advance preparation and prompt recognition. Good models can help at each step. Models are tools to assist - not replace -critical thinking, and to help in deciding which questions are most important. Model-making reminds us to make our assumptions explicit and to examine wide arrays of options and consequences.

Discussion

Smallpox

Several issues with regard to smallpox modeling arose during the presentations and in discussion. One set of issues had to do with inputs/ assumptions of the models. For example, the Ro (the number of people a contagious individual would infect) was thought to be quite high by some investigators based upon the 1972 smallpox outbreak in Yugoslavia or an earlier outbreak in Bangladesh, whereas other investigators believed that the Ro should be much lower, perhaps less than 3. The Ro number chosen for a model is important because the higher the Ro, the faster an epidemic will spread and the greater the likelihood that it will escape public health efforts at control. As a result, a higher Ro for smallpox will lead to a prediction of far more affected individuals and far more casualties than if a lower Ro is employed. Indeed, Dr. Penn pointed out that for many of the parameters in the models considered, there is considerable uncertainty.

Another matter was the assumption of uniform mixing of people by some models, e.g. those of Dr. Houston Dewey and Dr. Martin Meltzer. This assumption – that individuals in society uniformly associate with and infect one another -- is a major problem because standard public health policy for smallpox outbreaks is predicated upon a lack of uniform mixing. Indeed, public health policy stresses that contacts of contagious people should be identified and rapidly vaccinated to prevent them from becoming ill and from further spreading disease to secondary contacts. In his presentation, Dr. Charles Penn discussed differences between homogeneous mixing and viewing the population as consisting of individual cells in which contagious individuals may infect adjacent cells. Dr. Greg Wilson's EpiSims model presented at this meeting will not assume uniform mixing. Indeed, that model of the spread of smallpox pays careful attention to contacts of infected and contagious individuals in the home, workplace, during transportation, at school, etc. The EpiSims approach may come closer to the standard public health approaches than the two that assume homogeneous mixing. Dr. Greg Wilson predicted that combined use of contact vaccination plus quarantine could stop an epidemic before the third wave of contact illness (the initial cases would infect secondary cases but the secondary cases would not infect tertiary cases). This is consistent with CDC policy.

Dr. McKenzie felt that an assumption of uniform mixing works well enough in some circumstances and/or scenarios, but that more complex representations of individual-individual contact are necessary in others. Determining when the latter might be needed is a critical open research question, one that could be assisted with modest, well-directed resources.

At another meeting on modeling of bioterrorism agents that took place at Rutgers at the end of March, 2002, Dr. Edward Kaplan from Yale University presented a smallpox disease transmission and intervention model. He suggested that contact vaccination was based upon two factors: (a) World Health Organization smallpox eradication procedures in which there was substantial "herd immunity," and (b) venereal disease control in which contact therapy works because there is much slower disease spread. His results suggest that mass vaccination would stem an epidemic faster than contact vaccination. In contrast, recent smallpox modeling work by Drs. Ira Longini and Betz Halloran at Emory University suggests that: (a) assuming uniform mixing overestimates the number of contacts, and (b) contact vaccination is useful in stemming a smallpox epidemic. Longini and Halloran are modeling smallpox using an idealized city they have previously used for modeling influenza. They use a contact model with comparison of mass vaccination vs contact vaccination, and they also assess the effects of quarantine. They believe that the Ro for smallpox is about 3 and may be less for US in 2002 than in other situations. They do not like the random mix assumption of Dr. Edward Kaplan, Dr. Martin Meltzer and others.

The issue of quarantine for individuals infected with smallpox involves both time-honored public health practice and political considerations of people wishing to express their rights to go where they wish. Dr. Penn at this meeting indicated that the UK approach would be a combination of quarantine and contact vaccination, but that delays in implementation would lead to increased numbers of casualties. Dr. Merkle indicated that the same held for the U.S.: delays in vaccination would lead to much greater numbers of affected individuals. Dr. Meltzer also found that both vaccination and quarantine would serve to limit an outbreak; however, the largest "driver" in his model was the value of Ro. A low Ro of 2 would allow public health measures to control the outbreak whereas a high Ro of 5 would lead to many tens of millions of cases and great difficulty in controlling the epidemic. In Dr. Meltzer's model, only modest quarantine (25%) and vaccination rates (33%) were needed to keep the numbers of infected individuals low as long as the Ro was not too high (Ro = 3) and the number of initially infected people was not too high (n = 100).

Dr. Houston Dewey assessed the effect of quarantine in his model and found that quarantine would provide a benefit – in reducing the total number of affected – but that a major degree of compliance would be required. Indeed, several other scientists indicated that a substantial degree of compliance with quarantine would be highly desirable in reducing the spread of disease. However, concern was expressed regarding he political likelihood of quarantine being enforceable.

Recent publications in the New England Journal of Medicine are also relevant to the issues discussed. It was found that dilution of the current vaccines may still provide adequate protection, allowing a limited amount of vaccine to be used in more people (NEJM 346:1265 and NEJM 346:1275). An editorial on the vaccine issues is also found there (NEJM 346:1319). A review of clinical smallpox was published as well (NEJM 346:1300).

Anthrax

Mr. Bauer presented an anthrax model that predicted, for 15 liters/minute breathing, a median effective dose of 8,000 spores (LD50), and a probit slope of 1.0, that the LD5 (the dose required to kill 5% of exposed individuals) would be 182 spores. Dr. Houston Dewey also discussed anthrax dose-response curves. He pointed out that whereas a CW agent might have a very narrow dose-response curve, such that the dose to kill 5% of people was very close to the dose to kill 95% of people, anthrax had a much broader dose-response curve. As a result, the well-publicized LD50 of 8,000 spores for inhalation anthrax does not give a complete picture of the dose-response curve. Indeed, Dr. Dewey found that the LD10 for anthrax (the dose needed to kill 10% of individuals) was approximately 120 spores and the LD90 was approximately 500,000 spores. We noted that the LD5 to LD10 of Bauer and Dewey, arrived at by different models, were both under 200 spores. Thus, a relatively small number of spores may be lethal to a percentage of those exposed.

Indeed, for Salmonella, whereas the LD50 may be 10,000 cells, the LD10 may be as little as ten cells (Rev. Infect. Dis. 4:1096-1106, 1982). The anthrax LD7 for monkeys was approximately 300 spores when the LD44 was about 5,000 spores (Bacteriological Rev. 30: 657-659, 1966). A recent paper in the medical literature also discussed the possibility that a relatively low anthrax spore dose might infect a percentage of the population (Inglesby TV O'toole T, Hendearson DA et al Anthrax as a biological weapon. JAMA 287:2236-2252, May 1 2002). And another suggests that as few as 1-3 spores may be infectious (Peters C. J. Hartley D. M. Anthrax Inhalation. Lancet 359;710-711, 2002.)

Dr. Fred Harper presented a model of casualties after a release of anthrax over New York City or Los Angeles. A worst case scenario might lead to 438,000 fatalities in New York and 150,000 fatalities in Los Angeles, depending upon meteorological conditions. An anthrax release over a baseball stadium could result in up to 51,800 fatalities under stable meteorological conditions and up to 171,000 fatalities (including individuals outside of the stadium) under less stable meteorological conditions.

Ms. Burr pointed out that after a battlefield anthrax attack, early detection by some method other than clinical symptoms would largely eliminate casualties. However, if the first indication that an attack had occurred is illness in 2% of affected individuals, the time to diagnosis would be great enough so that medical intervention would come too late to prevent many of the casualties. Thus, rapid, early diagnosis is critical to a favorable outcome after exposure to inhalation anthrax.

A recent publication (Webb GF and Blaser MJ Mailborne transmission of anthrax: Modeling and implications. Proc. Natl. Acad. Sci. US 99: 7027-7032, May 2002) dealt with issues surrounding the use of the mails to transmit anthrax spores. In particular, it addresses the issue of cross-contamination of letters. The model assumes that as anthrax-filled letters move through the US Postal system, some anthrax spores leak out of the envelopes and that additional letters are contaminated secondarily. This phenomenon thus "proliferates" the number of contaminated letters. The authors postulate that secondarily contaminated letters could contaminate tertiary letters. Indeed, they suggest that an anthrax-filled envelope (a primarily contaminated letter) affected other letters that went through a US postal service machine within a one minute period of the filled, primary letter. These secondarily contaminated letters may have gone on to contaminate tertiary letters. The authors postulate that the woman in Connecticut who died of inhalation anthrax but had not received a letter that had gone though the machine within one minute of a known filled letter may have received a letter that had been in contact with a secondarily contaminated envelope. However, the wind was blowing from the Trenton NJ postal facility on October 9 directly toward the two individuals in the Bronx and Connecticut whose disease has remained unexplained. Thus, it is possible that airborne transmission might answer the mystery. Nonetheless, the authors' model indicates that if the Postal Service had received 100 primary letters (containing anthrax spores), the system might have generated millions of cross-contaminated letters and thousands of anthrax infections.

Plague

There is greater decay of vegetative forms of bacteria than of spores. Thus, *Yersinia pestis*, the organism that causes plague, which exists only in the vegetative form, is more readily degraded in the atmosphere than are the spores of *Bacillus anthracis.*

Dr. Heinbokel's model dealt with a deployed military unit. Modeling of plague released into the atmosphere must take into account such decay. After exposure to plague release, a 10,000 soldier unit might be reduced to as few as 2,000 functioning soldiers.

Ms. Burr's model demonstrated that rapid detection of a release of plague organisms could largely prevent casualties, whereas a delay in diagnosis until clinical signs and symptoms occur in exposed and affected individuals would prevent fewer casualties.

In the model presented by Ms. Giovachino, which assumed an Ro of 2, intervention by day 2 was the most important factor. This agreed with Ms. Burr's findings. Ms. Giovachino also found that quarantine of at least 75% was also helpful in reducing casualties. Dr. Davis's more complex disease propagation model of the natural spread of plague was most relevant to the natural transmission of plague.

Tularemia

There is greater decay of vegetative forms of bacteria than of spores. Thus, *Francisella tularensis*, the organism that causes tularemia, like *Yersinia pestis*, exists only in the vegetative form and is degraded in the atmosphere. Modeling of tularemia must take into account such decay.

Ms. Burr's model demonstrated that rapid detection of a release of *Francicella tularensis* organisms could largely prevent casualties, whereas a delay in diagnosis until clinical signs and symptoms occur in exposed and affected individuals would prevent fewer casualties.

Dr. Fred Harper's scenarios, which assumed an infectious dose of 30 CFUs and a lethality of .35, included releases of tularemia organisms over New York City or Los Angeles. A worst case scenario would lead to as many as 175,000 fatalities in New York and 29,300 fatalities in LA.

Appendix A. Speakers

Richard Babarsky
National Ground Intelligence Center (NGIC)

Mr. Timothy J. Bauer
NSWC, US Navy

John Bombardt
Institute for Defense Analysis (IDA)

Dr. Jay Boris
Naval Research Laboratory

Dr. John Brockmann
Sandia National Laboratories

Ms. Julia Burr
Institute for Defense Analyses (IDA)

Dr. Neil Carey
CAN Corporation (CANC)

Dr. Carlos Castillo-Chavez
Cornell University

Dr. Tim Carpenter
University of California, Davis

Dr. Jonathan Davis
Dynamics Technology, Inc.

Houston Dewey
Central Intelligence Agency

Dr. Lawrence Gershwin, National Intelligence Officer for Science and Technology
National Intelligence Council (NIC)

Ms. Monica Giovachino
CAN Corporation, SNAC

Dr. Richard Griffith
Sandia National Laboratories

Dr. Fred Harper
Sandia National Laboratories

Dr. John Heinbokel
Center for Interdisciplinary Excellence in Systems Dynamics, LLP

Dr. James Koopman
University of Michigan

Dr. James Kvach, Chief Scientist
Armed Forces Medical Intelligence Center (AFMIC)

Dr. Ellis McKenzie
Fogarty Center, National Institute of Health (NIH)

Martin Meltzer
Centers for Disease Control and Prevention (CDC)

Peter Merkle
Defense Threat Reduction Agency (DTRA)

Charles Penn
Center for Applied Microbiology & Research (CAMR), Porton Down, UK

Dr. Jeff Potash
Center for Interdisciplinary Excellence in Systems Dynamics, LLP

Dr. Fred Roberts
Rutgers University

Dr. Alfred D. Steinberg
The MITRE Corporation

Dr. Mark Thurmond
University of California, Davis

Dr. Greg Wilson
Los Alamos National Laboratory

Dr. James M. Wilson
Remotely Sensed Epidemic Intelligence (RESPI)