Center for Advancing Microbial Risk Assessment
Year-4 Annual Report

Submitted to

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And

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5-page Summary Annual Report

Center for Advancing Microbial Risk Assessment (CAMRA)

EPA Agreement: RD832262
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Introduction:
The science for understanding and preparing for any potential biological attack is also important for addressing any of the infectious agents and the subsequent diseases where the transmission is of national and global concern. Health security is currently on the public's mind today as the debate over health care ensues and biological agents such as influenza H1N1, norovirus, *Mycobacterium* tuberculosis, and antibiotic resistant *Staphlococcus* continue causing major concerns for schools, airlines, hospitals, nursing homes, and the public at large. What is the risk of disease spreading in our communities, in our schools to our children? What biological agents represent the greatest risk associated with contaminated indoor environments, our water or our food? How do we respond and control and most importantly prevent these infectious diseases when vaccines are not available or limited? The Center for Advancing Microbial Risk Assessment (CAMRA) is dedicated to addressing these questions and establishing approaches to promote US Public Health Security.

CAMRA was established in September, 2005 to advance quantitative microbial risk assessment (QMRA) data, tools, models and frameworks as well as the understanding and application of QMRA. The two major missions are focused on: 1) the technical science of; and 2) knowledge management and exchange. This is the only Center of Excellence jointly funded by EPA and DHS which is addressing and developing the technical information necessary for QMRA. CAMRA is modifying the National Academy of Science chemical risk assessment framework to address infectious agents and provides evidence-based science for the development of sound policies by regulatory agencies including EPA, DHS, and others. CAMRA has been established as four main research projects which have further developed the NAS QMRA framework including Project I: Exposure Assessment; Project II: Infectious Disease Transmission; Project III: Dose-Response; and Project IV: Risk Characterization, Communication, Integration of QMRA Science, and CAMRA specifically developed Project V: Knowledge Management and QMRA education.

EPA, DHS and other agencies (CDC, USDA, and state agencies) are developing policies for environmental monitoring and clean up after natural disasters or terrorist attacks. In four years, CAMRA has addressed a new QMRA paradigm (Projects II, IV and V) that includes specific dose-response models (available from Project III for all the class A agents) and key information on pathogen survival and transmission (provided by Project I) which allows one to address risk, management options and communication strategies associated with human behavior (Project IV). .

CAMRA has provided a "quantitative yard stick" that can be used to judge the level of the microbial threats. This has always been a major limitation for managing microbial threats. Figure 1 below shows the expansion and development of the CAMRA QMRA framework. This

has been used to determine that the characterization and management of risk is venue and scenario specific. Thus CAMRA is working to develop risk assessments where key components are central to the understanding of the risk and developing a system adaptive to the emergent problem so that it can be addressed rapidly.

Figure 1. Expansion of risk assessment framework for understanding the potency, venue and scenario specific nature of the microbial hazard and disease transmission.
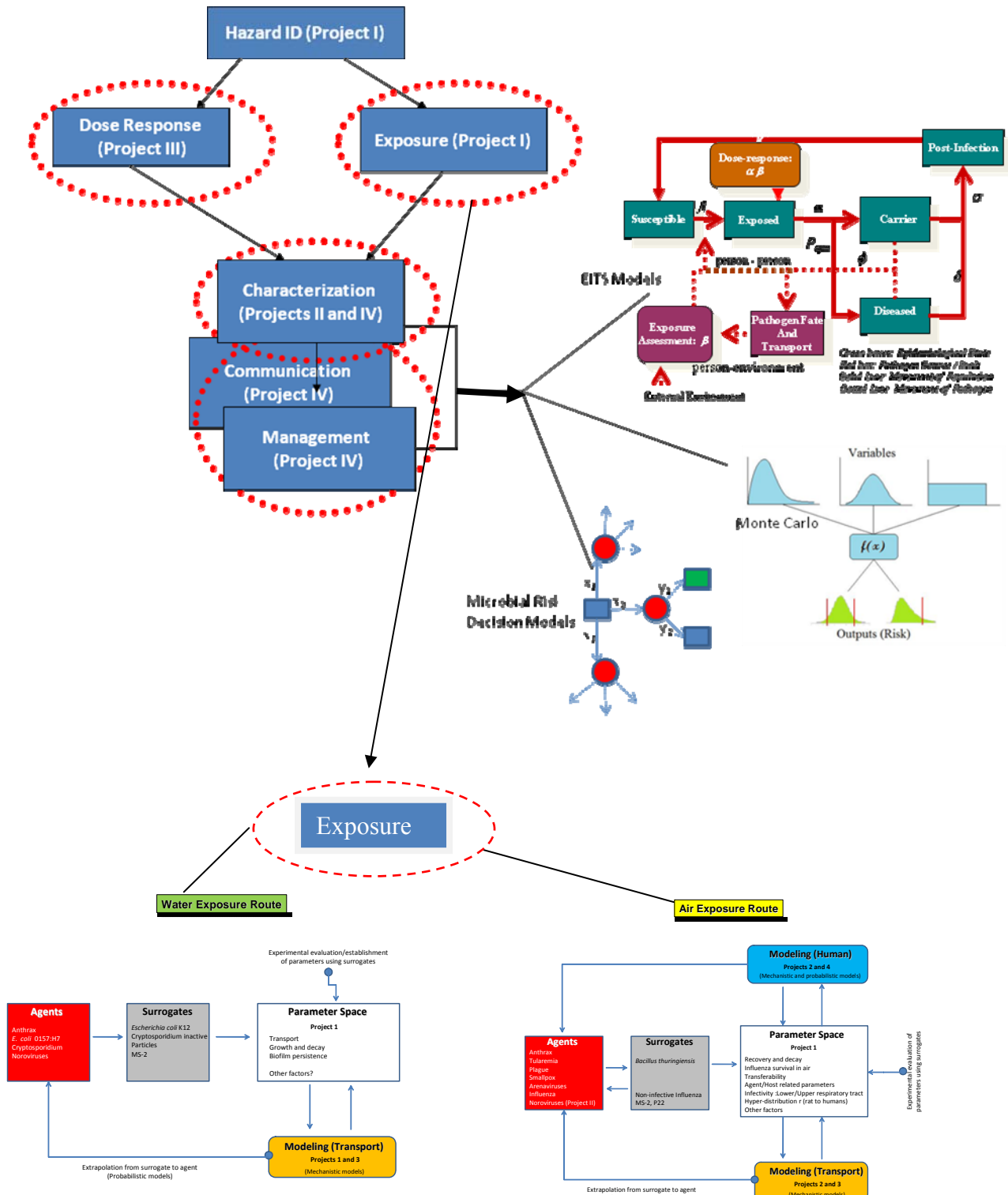
Summary of Key Findings and Accomplishments

CAMRA's high productivity after four years has now reached an exciting level of maturity in which the frameworks and assessments are being integrated into the research by all PIs and projects. The knowledge gained has been presented to the risk community through 13 publications and 18 presentations. The next generation of QMRA students are now graduating and entering the workforce. CAMRA will continue this high output for the coming year. Table 1 below quantifies some key accomplishments.

Accomplishment Type	Amount
Peer reviewed publications	11
Peer reviewed proceedings	2
Master's theses	2
Doctoral theses	1
Un-referred articles	3
Conference presentations	18
CAMRA workshops	4th QMRA Summer Institute • 25 Students (2 government, 2 private companies, 20 academic) • 5 nations (Canada, Israel, Egypt, S. Korea, United States)
Supported students	15
Students graduated	4
Year 4 Things in Progress Learning Units	84
Year 4 Things I Have Completed Learning Units	23
Year 4 learning units showing associations	27

CAMRA Project I has published an expansion of the understanding of the axial transport of *Escherichia coli* (*E.coli*), MS-2 virus and *Bacillus thuringiensis* (*B. thuringiensis*) in drinking water systems. This is adding to an improved ability to address who is at risk and where to place sensors in the system. A tool for describing survival data has been produced. Project I has also begun work on transfer efficiencies from fomites to skin, as well as determining the effect of exposure route on the associated risk. Finally, an approach to use and understanding molecular signals and limits of the detection methods for describing risk has been developed.

Currently working on influenza, Project II has examined the effects of biological and environmental conditions and is elucidating the dominant modes of disease transmission via air, or fomite hand interactions. This determination of the effects of the biology of the host and the interaction with the environment can now be easily adapted to other viruses, such as smallpox and avian flu. Project II has also addressed how viruses (Norovirus in this case) are transmitted among family groups. This marks a first step on expanding our knowledge of how viruses and other pathogens move through communities. Project II is now looking at how multiple doses and timing of these exposures to different doses affect the predicted response of the host.

CAMRA, via Project III, has developed dose-response models for the category A agents (*i.e. B. anthracis*, *Variola major* (smallpox), *Yersinia pestis*, Ebola, Marburg, Lassa) as well as category B agents (i.e. Brucellosis, Q-fever) and has addressed *Francisella tularensis* associated with ingestion and multiple exposures. The first framework for physiologically based dose

response models, currently specific to inhalation anthrax has been developed which informs how the host and the pathogen interact with each other. Also Project III has developed the first inclusion of time post inoculation into dose response models which allows for great advancements in understanding how the body reacts to pathogen exposure and paves the way for understanding multiple dosing of pathogens effect on the host. These models, generated by CAMRA researchers, allow more exact quantitative evaluation of risks based on levels of pathogens.

Project IV has been able to utilize the CAMRA information from the other projects and develop decision science based approaches for determining the safety level focusing on Anthrax. Project IV has developed a number of response and remediation strategies for determining "how clean is safe". These strategies will be used to inform future decision models in order to react to potential malicious releases, which will reduce the risk appreciably as well as being as efficient as possible with the remediation schemes. Project IV has also been performing semi-structured interviews which allows for elucidation of how people's knowledge influence their behavior in regard to public health information and risk. The understanding of how disease and flu specifically in this case, is transmitted and how to prevent transmission was the focus of the study. This information is vital to being able to instruct potential victims and their families of how to prevent the spread of disease and recover if they are exposed.

Project V has continued to focus on understanding the risk field with the inputs into the Knowledge Repository System. Personnel have begun working with CAMRA researchers on the development of the data warehouse, one of the main products associated with CAMRA work. This store house will allow one to access critical data (both processed and raw data) for modeling and undertaking QMRA as well as produce a site where the QMRA field can expand.

Project Specific Reports

Project I: Exposure: Detection, Fate and Transport of Biological Agents of Concern (BAC)

One of the greatest challenges in assessing the risk from microbial agents is in predicting the exposure with a quantitative output that can be used in the risk characterizations for specific environments or venues (e.g. building, drinking water). Project I activities are designed not only to provide the data that can be used for exposure assessment in risk models, but also to provide a basis for using data from environmental samples in risk assessment and to develop surrogates for bio-threat agents that can be used in developing fate and transport models. Project I key work includes both a focus on the water venue and the indoor environment addressing the roles of fomites and hands

In order to better predict exposure to bio-threat agents in drinking water distribution systems, axial dispersion coefficients used in one-dimensional solute transport equations were developed from experimental data using *E. coli*, MS-2 virus and *Bacillus thuringiensis* spores. This information is also being used to assess the impact of various levels of contamination in water for the optimal placement of real time sensors within drinking water distribution systems. In conjunction with this work neural networks are being assessed to identify the location and time of a contaminate intrusion in a portable distribution system.

Studies have developed a tool in Microsoft Excel that can be used to analyze survival data to examine the rapid die-off during droplet drying and then stability of the biological particle. Survival may be dependent on the porosity of the fomite and relative humidity in the

indoor environment. Currently new studies are underway to determine the transfer coefficients of bacteria, viruses and spores from different types of fomites, survival on skin and transfer from skin to skin. This information is needed to provide data for indoor exposure models for fomite contamination, which will feed into the frameworks of Project II's.

The potential relative impacts of different exposure routes (inhalation, fomite, direct contact and droplet to skin) have been have been developed for influenza virus. Further research is underway to reduce the uncertainly in these types of models by collecting data on frequency of coughing, sneezing and frequency and concentration of organism within the droplets produced. In addition, work is underway to determine the fraction of cough particles that strikes the eyes, nostrils, and lips of a person in close contact.

Genetic characterization of highly touched and untouched fomites is ongoing to analyze microbial dispersion data. This will provide assessment of the background bacterial populations at touched and untouched surfaces as illustrated by their 16S rRNA gene. The Influenza Fomite Sampling Project from the University of Michigan provided the samples taken from highly touched and untouched fomites in dormitories. This project will begin to provide a "Molecular picture of risk".

After addressing the risk estimates that can be made based on monitoring of anthrax with environmental detection limits, project I is now exploring the limits of risk detection for viruses in a similar fashion.

Project II: Infectious Disease Models for Assessing Microbial Risks for Developing Control Strategies

Over this past year, Project II has pursued three overall objectives: 1) to develop a framework for analyzing environmental infection transmission systems (EITS); 2) to develop tools for model identification and model choice; and 3) to develop tools for analysis of intervention and control options.

Specifically, with regards to the first objective a framework document has been published in the *American Journal of Epidemiology*, entitled: Dynamics and control of infections transmitted from person to person through the environment. A context to examine the role of the environment in pathogen transmission and a framework to interpret environmental data to inform environmental interventions was provided. Based on this framework, one can now examine the different biological and environmental contexts that determine the dominant modes of transmission for influenza (*e.g*. Addressing the current issues surrounding the role of respiratory transmission vs. the role of fomites and hands). This work helps inform decision makers about intervention options for conditions like the current H1N1 pandemic. By the end of 2009 this novel framework will be applied in examining three specific interventions for controlling influenza spread: hand hygiene, decontamination, and masks. In parallel to this work, the original framework has been extended to include multiple venues and human movement patterns. This has led to a more extensive and operational classification of fomites involved in transmission and allows examination of intervention options for a broader range of contexts such as community level spread among households, schools, and workplaces.

With regards to the second objective, a statistical analysis of within household norovirus transmission that generally occurs after a point source outbreak event provides insight into the ability of norovirus to spread into households after a community outbreak.

The final accomplishment has been to take the dynamic dose response models developed in Years 2 and 3 and use them to analyze a published data set of inhalation anthrax death in

monkeys due to temporal patterns of exposure. This analysis provides: 1) an approach to assessing the risks associated with exposures that vary over time; 2) evidence that dose timing and dose order matters with respect to risk estimates; and 3) a tool for helping to design additional multiple dosing studies that can further inform us on the importance of dose timing and order and provide data to help refine dynamic dose response models. In Year 5 the framework for assessing risks using environmental infection transmission models will be further refined and applied to important public health problems.

Project III: Dose Response Modeling and Application

Dose-response relationships and models are a central critical component of a QMRA regardless of the risk characterization/management approach used. CAMRA now has the largest collective set of dose-response models for Class A and B pathogens.

The accomplishments include the largest number of reviews of dose response relationships by any group for pathogens of concern. Many of these reviews have been published, submitted for publication or presented at meetings. These relationships describe and can be used to address how the risk of an adverse event varies with the dose of an infectious agent. These relationships are now being used to advance the QMRA.

- In the event of a release of an agent, the risk to the population from the exposure (based on exposure estimates from Project I) is being computed, currently focusing on *Cryptosporidium* in water distribution systems, as well as anthrax in the indoor environment.
- The residual concentration of an agent after remediation from an incident was used to compute a residual risk, and in conjunction with work from Project IV was used to assess the appropriate level of response to an incident

During the past year, updated dose response models for *Bacillus anthracis*, influenza A virus, *Coxiella burnetiii* (Q Fever), equine encephalitis viruses, and coronaviruses were developed. Particularly important has been the development of models incorporating time to effect (i.e. what is the time distribution of cases following an exposure to an agent). This work includes data on *Yersinia pestis*, *Francisella tularensis, Mycobacterium tuberculosis* and *Bacillus anthracis*. With respect to the latter, the consistency of animal derived dose-response-time data for *B. anthracis* with the time to effect data from the Sverdlovsk USSR incident have been analyzed. This work is illuminating two important issues: 1)How does the concentration of an incident after release influence the time for effects in the exposed population to be realized? This will inform the range of time available for first responders depending on the potency of the agent and the initial dose; and 2)The residual contamination that exists after a release exposes individuals repeatedly to lower doses and a better understanding of what this means for clean up goals and re-entry criteria for buildings is needed.

A physiologically based dose response model for *B. anthracis* incorporating both physical factors and biological factors governing the fate, transport, growth and decay of the bacterium in the human respiratory tract has now been developed leading to a doctoral dissertation.

The project III team at Drexel has been working with the project III team at Michigan State to obtain new experimental data on the response of animals to ingestion of *Francisella tularensis* that will be used for the development of improved dose response time models. By

comparison of the data obtained in these explicitly designed experiments with the data from the literature on inhalation dose response, extrapolation of risks between different portals of entry can be performed.

During the forthcoming year, dose-response modeling of rickettsial organisms will be finished and the   dose response time modeling will be extended to model response to multiple doses of organisms. The Drexel-Michigan State group generating *Franciscella tularensis* data will plan and analyze the experiments. More integrative QMRAs will be undertaken working with the Project IV team for decision making. A greater focus will be on the search for outbreak data that can be used to validate the dose response and dose-response-time models.

Project IV: Assessment-Analysis Interface

Project IV researchers at Drexel continue to work on developing response and remediation standards for *B. anthracis* spores. Three important results have been described and will be useful for decision makers. The first describes the approach used to develop quantitative standards for surfaces and ventilation system filters, the second identifies important uncertainties in the approach, and a third describes how environmental sampling may be used to identify the particulate size fractions of a release. These will allow for better decisions about when to monitor, what the data may mean and how both the air system and the surfaces influence the risk. Finally, by understanding the uncertainties one can place one's efforts in areas that will significantly improve the risk estimates and the decisions that need to be made. Additional work describes the development of risk-based sampling schemes for air which will assist in determining allocation of resources. All of these efforts represent technical risk assessment input in the question of "how clean is safe?" and may help to prioritize sampling and remediation efforts and interpret the results of environmental monitoring by providing a link between measured concentrations and human health risk. Future efforts are planned to broaden this approach beyond *B. anthracis* to a variety of other organisms, using dose-response models developed by CAMRA's Project III and estimates of persistence developed by CAMRA's Project I.

The standard development effort will be further informed by ongoing work developing risk-based decision criteria for common response actions for a *B. anthracis* release, including vaccination, antibiotic prophylaxis, and environmental remediation. This work uses a benefit-cost framework to identify circumstances where such response actions are helpful and circumstances where risks are so small that response actions may not be justified based on benefit-cost assessment.

Researchers at Carnegie Mellon University completed semi-structured interviews to assess public understanding of flu transmission risk factors. This effort has now developed a database suitable for statistical analysis. Over the next year, the analysis of this database and a confirmatory structured survey will be completed. This effort will identify key gaps in public understanding that can be targeted by future risk communication efforts. Improving public knowledge of influenza transmission has to potential to improve public compliance with guidance from public health authorities and reduce the spread of influenza and similar infectious diseases.

Project V: Knowledge Management, Learning and Discover

Project V in Year 4 completed the design and implementation of the CAMRA Knowledge Repository. Several features are now available to all investigators, while we conduct the final tests and users learn how to benefit from all system capabilities. The collaborations with investigators from all Projects I through IV and their use of the system have promoted integration in a way that the group is now ready to work on a product that will be made available to all QMRA community.

The fourth QMRA Summer Institute was run in 2009. A total of 25 students attended from 5 nations (Canada, Israel, Egypt, South Korea and the United States). The students participated in lectures, exercises, and most importantly case studies. The case studies as summarized below incorporate a range of human health concerns and a number of interesting results and recommendations.

Influenza

The case study team used an influenza transmission model developed by Project II based in the NetLogo language. The students used this model to determine the number of students who are infected, recovered and immune and those which are available for infection. Overall the case study group determined that the combination of surface decontamination and wearing protective masks are the best and most cost effective means of preventing the spread of influenza in the elementary school environment.

Bocavirus

Human bocavirus is a recently discovered virus which affects humans, typically the young. A case study was developed to determine the risks to the young children and workers at daycare facilities. The students developed a Markov chain model, which models the cough frequency and the amount of bocavirus which is being dispersed around the room (ageneric box room). Using this model the group determined the level of risk to the workers as well as the children in the facility, showing a fairly significant risk to the young children in the facility (> 10-3). The group also found that for new pathogen the most important data and knowledge gaps which should be filled, include dose response models specific to bocavirus, better sampling and detection measures for quantifying bocavirus in human excretions in the environment.

Pet and Human Health

This case study was based on understanding better the connection between the health of the pets and that of their owners. The case study team decided to look at *Salmonella* specifically delivered from small turtles and was able to show that owners of pets were incurring a greater risk than those who do not have pets in their home (based on some extrapolations to multiple pet species and the limited literature on zoonotic pet disease transmission). This case study was not extrapolated to areas outside of the home (kennels, veterinarians, etc.). The case study group also determined that a good hand washing strategy was the best means of intervention. The study also determined that the main factor influencing the risk of infection was due to the concentration of *Salmonella* in the turtle's feces and fairly high excretion rates.

Anthrax Outdoor Release

This case study group was challenged with determining the risk associated with a Clean-up response to an outdoor Anthrax attack in the financial district in Seattle Washington. The group determined the amount of water necessary to wash down the square footage of building that would protect the workers and citizens who may be moving through the attack area. This involved understanding the dispersion in the air as well as the requisite risk levels. The group

also needed to take into account the dispersion within the Puget Sound to determine the risk to recreational and commercial users of the Sound from the runoff of the wash water. This overall risk assessment was an ambitious goal for the case study group which determined that there may be enough time available after the event during the clean up, to establish a temporary treatment system at the runoff outfall.

Appendix A: Summary of Accomplishments

Publications

(Peer reviewed journals)

Corella-Barud, V., K.D. Mena, S.G. Gibbs, P.L. Gurian, and A. Barud. (2009). Evaluation of Neighborhood Treatment Systems for Potable Water Supply. International Journal of Environmental Health Research, 19(1):49-58

Durham D.P.and Casman, E. A. (In Press) Threshold Conditions for Bubonic Plague Persistence in Urban Rats. Risk Analysis.

Herzog AB, McLennan SD, Pandey AK, Gerba CP, Haas CN, Rose JB, Hashsham SA.(2009). Implications of Limits of Detection of Various Methods for *Bacillus anthracis* in Computing Risk to Human Health. Applied Environmental Microbiology. 75:6331-6339

Huang, Y., Bartrand, T.A., Haas, C.N. and Weir M.H. (2009) Incorporating Time Post Inoculation into a Dose-Response Model of *Yersinia pestis* in Mice. Journal of Applied Microbiology. 107(3):727-735.

Huang, Y. and Haas, C.N. (2009) Time-dose-response Models for Microbial Risk Assessment. Risk Analysis. 29(5): 648-661.

Huang, Y., Hong, T., Bartrand, T.A., Gurian, P.L., Haas, C.N., Liu, R., and Tamrakar, S.B. (2009) How Sensitive Is Safe? Risk-Based Targets for Ambient Monitoring of Pathogens. IEEE Sensors Journal. Accepted for publication.

Huang, Y., Hong, T., Bartrand, T.A., Gurian, P.L., Haas, C.N., Liu, R., and Tamrakar, S.B. (2009) How Sensitive Is Safe? Risk-Based Targets for Ambient Monitoring of Pathogens. IEEE Sensors Journal. Accepted for publication.

Jones, R.M., Masago, Y., Bartrand, Haas, C.N., Nicas, M., and J.B. Rose. (2009) Characterizing the risk of infection from *Mycobacterium tuberculosis* in commercial passenger aircraft using quantitative microbial risk assessment. Risk Analysis. 29, page 355.

Jones R. and Nicas, M, (2009) Experimental Determination of supermicrometer particle fate subsequent to a point release within a room under natural and forced mixing. Aerosol Science and Technology. 43: 921-938.

Sinclair, R., Gomez, P.R., Choi, C.Y., Gerba, C.P. (2009) Assessment of MS-2 phage and salt tracers to characterize axial dispersion in water distribution systems. Journal of Environmental Science and Health. 44: 963-971.

Weir M.H., Haas, C.N. (In Press) Quantifying the Effect of Age on the Dose Response of *Variola major* in Suckling Mice. Human and Ecological Risk Assessment.

(Peer Reviewed Proceedings)

Gunawardena, S., & Weber, R. (2009). Discovering Patterns of Collaboration for Recommendation. In Proceedings 22th International FLAIRS Conference, FLAIRS`09. AAAI Press, Menlo Park, California, 2009.

Gunawardena, S., & Weber, R. Paper presented at FLAIRS conference. (2009) Discovering Patterns of Collaboration for Recommendation. Proceedings: 22nd International FLAIRS Conference, FLAIRS`09. AAAI Press, Menlo Park, California, 2009.

(Book Chapters)
none

(Theses / Dissertations)

1. Ms. Surakshya Dhakal, University of California Berkeley, 2009 Masters Thesis. Exploring the Relationships between Time-to-Mixing, Turbulence Intensity, and the Turbulent Diffusion Coefficient. Supervised by Professor Mark Nicas.
2. Tao Hong, Drexel University, 2009 Masters Thesis. Estimating risk of exposure to *Bacillus anthracis* based on environmental concentrations. Supervised by Patrick Gurian
3. Mark H. Weir, Drexel University, 2009. Doctoral Dissertation. Development of a Physiologically Based Pathogen Transport and Kinetics Model for Inhalation of *Bacillus anthracis* spores. Supervised by Charles N. Haas

(Un-refereed documents)

White Paper Submitted in Support of the Physiologic Assessment of Microbial Effects (PhAME) Project.

White-Paper was submitted to USACCHPM and is currently pending security clearance for public release of the information. Jade Mitchell-Blackwood and Patrick L. Gurian, Development of Dose-Response Curves for *Bacillus anthracis* (Inhalation Anthrax) Using a Bayesian Approach on Historic Data.

White Paper Submitted in Support of the Physiologic Assessment of Microbial Effects (PhAME) Project, Limited Distribution through the U.S. Army Center for Health Promotion and Preventive Medicine, Environmental Health Risk Assessment Program (MCHB-TS-REH), Aberdeen Proving Ground, Maryland (2008).

Presentations
(Conference)

E. Casman. Risk Communication Planning for the Aftermath of a Plague Bioattack. Joint U.S. Environmental Protection Agency and Department of Homeland Security Conference on Real-World Applications and Solutions for Microbial Risk Assessment. Bethesda, MD. April 8-10, 2008.

Herzong A. *et al.* Validation of Detection Methods. CAMRA All PI Meeting. October 20-22, 2009.

Hong, T. Input-output correlation sensitivity analysis for environmental standards for *Bacillus anthracis* spores were evaluated based on assigned statistical distributions.

Huang Y., T. Hong, P. L. Gurian, C. N. Haas, T. Bartrand, S. Tamakar, and M. Weir. Benefit-cost analysis to develop targets for ambient air sampling. Society for Risk Analysis Annual Meeting. Boston, MA. December 7-10, 2008.

Huang, Y. and Haas, C.N. Dose-response Time Modeling. The Third Annual Department of Homeland Security University Network Summit on Research and Education. Washington DC. March 17-19, 2009.

Huang, Y and Haas, C.N. Quantification of the Temporal Effect on *Mycobacterium tuberculosis* Infection by Time-dependent Dose-response Models. 110th General Meeting of the American Society for Microbiology. Philadelphia, PA. May 17-21, 2009.

Mitchell-Blackwood, J. Benefit-cost assessment of the level of risk at which prophylactic antibiotic treatment of anthrax passes a benefit-cost test. Oral presentation at the Society of Risk Analysis Annual Meeting. Boston, MA. Dec. 2008. Winner of the Biological Stressors Student Merit Award.

Mitchell-Blackwood, J. Finding Risk Based Switchover Points for Response Decisions for Environmental Concentrations of *Bacillus anthracis*. Presentation at the Drexel Engineering Research Symposium. March 20, 2009.

Mitchell-Blackwood, J. Finding Risk-Based Switchover Points for Response Decisions for Environmental Exposure to *Bacillus anthracis*. Presentation at The Third Annual DHS University Network Summit. March 17-19, 2009.

Mitchell-Blackwood, J. Decision Science and Microbial Risk: Intervention Decision Modeling for Airborne *Bacillus anthracis* Release: Which Response and When? Presentation of results at CAMRA All PI Meeting at EPA. October 22, 2009.

Mitchell-Blackwod, J. Using an Economic Model to Inform Response Decisions for Environmental Concentrations of *B. anthracis.* Poster presented Association of Environmental Engineering and Science Professors Conference. Iowa City, Iowa. July 2009.

Nappier S., Weir M.H., Haas, C.N. A dose-response model for equine encephalitis viruses, with age susceptibility quantification. Poster presentation was given at the DHS student summit. March, 2009.

Weir M.H. and Haas C.N. Development of Physiologically Based Dose Response Models for Inhalational Anthrax; Society for Risk Analysis Annual Meeting. Baltimore Maryland. December, 2009.

Weir, M.H. and Haas C.N. Development of Physiologically Based Dose Response Models for Inhalational Anthrax; Association of Environmental Engineering and Science Professors.. Iowa City, Iowa. July 2009.

Weir M.H., Haas, C.N. Including Pathogenesis and Transport Physics for Inhalation Dose Response of *Bacillus anthracis*. Department of Homeland Security, Science and Technology Directorate, Office of University Programs. Annual University Network Summit on Research and Education. Washington DC. March, 2009.

Weir M.H. and Haas, C.N. Tularemia Dose Response Analysis for Oral Exposure of Multiple Strains. Department of Homeland Security, Science and Technology Directorate, Office of University Programs. Annual University Network Summit on Research and Education. Washington DC. March, 2009.

Weir M.H., Haas C.N. Microbial Dose Response Modeling for the 21st Century: Development of Mechanistic Dose Response Models. Society of Risk Analysis Annual Meeting. Boston, MA. December, 2008.

April Wright, Patrick L. Gurian, Hernando Perez, and David Greenberg. Bacterial Recovery from HVAC System Filters. American Society for Microbiology. Philadelphia, PA. May, 2009.

(CAMRA Workshops)

4th QMRA Summer Institute, Michigan State University, East Lansing, MI, 16-21 August 2009.

- Rose, JB: Microbes and Public Health
- Rose, JB: Introduction to Quantitative Microbial Risk Assessment
- Gurian, P: Statistics and Uncertainty
- Gurian, P: Maximum Likelihood Fitting
- Haas, CN: Animal Experiments vs. Epidemiological Study
- Haas, CN: Dose-Response Models
- Weir, M.H: Monte-Carlo Simulation and Crystal Ball® Use
- Rose, JB: Methods for Detection of Microorganisms: False Positives and False Negatives, Specificity and Sensitivity
- Gerba, CP: Exposure Assessment
- Gerba, CP: Measuring Microbes (Recovery & Inactivation)
- Medema, G: Fate & Transport Models: Water Distribution
- Haas, CN: Fate & Transport Models: Indoor Air/Fomites
- Koopman, JS: Infection Transmission Models
- Gurian, P: Risk Perception, Communication, and Management
- Gurian, P: Bootstrap Uncertainty Analysis

Appendix B: Knowledge Repository Summary Reports

CAMRA Report for Year IV (September 15, 2008 to September 14, 2009) for Project I

1. Project I
2. Investigators: Christopher Choi, Mark Nicas, David Wagner, Paul Keim, Ian Pepper, Syed Hashsham, Ryan Sinclair, Sonia Fankem, Tomoyuki Shibata, Rachael Jones, David David Greenburg , Scott McLennan , Pedro Romero, Ryan Austin, Yoshifumi Masago, Stephanie Boone, Amanda Herzog, Jessica Henley, Inhong Song, Alok Pandey, William McGarry, Andrew Lerch, Leilei Qian, Joan Rose, Charles Gerba
3. Project Goals:
   Development and validation of surrogates for bioterror agents.
   Development and validation of models for the survival, recovery, fate, and transport of infectious agents in the environment.
4. Tasks for Year IV (September 15, 2008 to September 14, 2009):

Dr. Charles P. Gerba's Laboratory (UA):

- **Fate and Transport of Microbial Agents via Fomites**
  - A workshop held last year among the principal investigators identified the need for data on the transfer of bio-threat agents from fomites to hand and from the hand to the other fomites. It was also noted that data was very limited on the survival of pathogenic microorganisms on hands (skin). The goal of year four is to address these data needs by a series of experiments. These data needs will be address in a series of experiments as outlined below.
    - **Transfer and survival experiments involving surrogate organisms**. In these experiments the transfer of non-pathogenic surrogates will be used to assess their transfer from contaminated hands to fomites, transfer from contaminated fomites to the hands and from contaminated hands to fomites. The following surrogate organisms will be studied:
      - Coliphage MS-2
      - *Escherichia coli*
      - *Bacillus thurengensis* spores (Their survival on the skin will also be determined.)
    - **Transfer and survival experiments involving vaccine influenza virus and human norovirus**. The experiments in phase one will be repeated using influenza virus, a human respiratory virus and norovirus, an enteric virus. Infectivity assays will be used for the vaccine influenza virus and UV light exposed human norovirus will be used and assayed by quantitative PCR.
    - **Assessment of human collagen artificial skin for use in transfer experiments involving bio-threat agents.** Collagen has been used to stimulate human skin and we propose to assess its use for transfer experiments. We purpose to compare the results obtained with agents in phase 1 and 2 on transfer with collagen to determine if similar results can be obtained. If successful collagen could be used in experiments involving bio-threat agents in year five of this project.
    - The following fomites will be tested:
      - Glass
      - Stainless Steel
      - Formica
      - Porcelain

- Polyester
- Cotton

- **Tasks for Year IV Based on Partial Funding**
  - When addressing biological agents, one of the limitations has been the inability to judge microbial risks with a "quantitative" yard stick. CAMRA is providing this yard stick by connecting dose-response models that can be used for threat ranking by everyone from first responders to assessors and remediators and by providing information on exposure including the survival of these important pathogens. CAMRA has begun to reveal the details of two important disease pathways (Figure 1). The first pathway, the water exposure route, focuses on survival, fate, and transport of BAC (biological agents of concern) within a water distribution system. It is clear that the distribution system is the most vulnerable to contamination and can pose the largest risk of spreading disease to a large population. The pathway has been difficult to monitor and clean up. The second pathway is associated with the air exposure route in the indoor environment and deals with the survival, fate, and transport of BAC, both in aerosols and on fomites. Monitoring this pathway requires dose-response information for inhalation and ingestion through hand-to-mouth transfer from fomites. The air exposure route includes person-to-person disease transmission and thus integrates human behavior into the risk assessment.

Dr. Christopher Choi's Laboratory (UA):

- **Dispersion of Microbial Agents in Drinking Water systems**
  - To access exposure via drinking water from the intentional release of bio-threat agents requires an understanding of the dispersion and mixing of these agents. Such information can also be used to determine where the agent was released into the distribution system. The following activities summarize the recent research progress, and tasks for October, 2008 through March, 2009 (the first 6 month period of Year IV) are summarized below.
    - Water distribution networks consist of numerous cross-, tee-, and wye- junction connectors. A series of experimental and numerical studies have sought to understand solute mixing at a cross junction. To address solute mixing phenomena at cross junctions, a fully functional computer program was developed based on experimental results. The code was validated using a set of network-level experimental data. Comprehensive solute mixing patterns are investigated for various combinations of cross, double-tee, and wye junction connectors with different flow directions. Mixing patterns for various junction configurations are also visualized by means of dye injections at different flow ratios.
    - The axial dispersion study examines the transport mechanisms of chemical and microbial tracers under various flow conditions in water distribution systems. Inlet concentration readings for a series of experiments were used as upstream boundary conditions for Computational Fluid Dynamics (CFD) simulations and 1D Advection-Dispersion (AD) models. The resulting downstream concentrations were compared with analytical approximations to determine the reliability of each approach. Additionally, experiments were carried out with surrogates; MS-2 and *E. coli* in particular. These studies indicate that microbes were significantly retarded and that the organism produced long tailing effects in the water after release.
    - The aforementioned findings have been integrated into a water quality solver suitable for large-scale network simulations and corresponding applications. For example, sensor network designs in water distribution networks have been

examined using the improved water quality model. The optimization algorithm minimizes the number of sensors needed for detecting potential microbial contaminant intrusions at all the nodes (100% detection coverage), while maximizing the redundancy of sensor coverage. Extended-period simulations of a set of contamination events were performed on the water quality model and resulted in distinct contamination-event matrices. Comparisons of the required number of sensors and corresponding locations indicate that incomplete mixing at pipe junctions has a significant impact on the optimal sensor placement.

- o Improved water quality models will be crucial in identifying optimal locations for water quality sensors, assessing models for early warning systems, and generating the exposure information needed for quantitative risk assessment. Experimental data compiled from in small-scale pipe networks was used to better refine existing models used for detecting contaminates in distribution systems and to allow for predicting concentrations of bio-threat agents within large scale complex drinking water distribution systems. Based on aforementioned research activities, we propose to conduct following research activities during the funding period from October, 2008 through March, 2009 (the first six-month period of Year 4).

  - **Dispersion of Microbial Surrogates:** Based on our experimental, computational, and analytical approaches, and in order to characterize axial dispersion in water distribution systems, we will finalize the examination of MS-2 bacteriophage as a surrogate. We are particularly interested in the relatively long tailing pattern of MS-2. The data will be summarized in a publishable format, and the manuscript will be submitted to a refereed journal for review. We intend to further analyze dispersion rates using Computational Fluid Dynamics (CFD) simulations as a function of the multiple parameters that characterize the flow, the fluid, the dissolved substance and the evolution of dispersion

  - **Optimal Real-time Sensor Placement and ANNs:** We demonstrated that using a water quality model that accounts for imperfect mixing (AZRED) at pipe intersections produces outcomes that differ from those produced by studies that assume perfect mixing. We hypothesized that these differences would consequently produce a different scheme for optimal sensor placement. The proposed work uses a multi-objective approach that relies on the non-dominated, sorted algorithm II. The study seeks, first, to contrast the use of the AZRED water-quality model to the use of water quality models that assume perfect mixing and second, to propose more efficient, less costly scheme for sensor placement. By using the simpler objective of optimizing for complete sensor coverage, the study will expand on previous work that made this comparison. An example network will be analyzed using both AZRED and EPANET, and the real-time sensor results will be compared. To identify contaminant release time and source locations, Artificial Neural Network schemes (ANNs) will be used.

  - **Risk Assessment due to Intrusion of *Cryptosporidium*:** To build *Cryptosporidium* outbreak scenarios in water systems, we will consider three water distribution networks: i) Network 1 in EPANET; ii) 5x5 network; and iii) Network 3 in EPANET. Using both EPANET and AZRED, we have thoroughly examined these networks in our previous and ongoing water quality modeling and sensor optimization studies. We found these to be suitable for examining and building outbreak scenarios for microbial risk assessment. At the beginning, to predict risks, we will create a few case studies using dose-response functions employing typical water demands. We will also consider two commonly-used

variables for sensor placement optimization (i.e. minimum hazard level (MHL) and minimum detection level (MDL)).

Dr. David Wagner's Laboratory (NAU):

- **Validation of a potential surrogate for *Bacillus anthracis***
    - o We have completed a thorough literature review and, based upon this review, identified the best possible surrogates. The next step is to choose among this short list of surrogates based upon information not available if the scientific literature. To this end, we are continuing with long-term experiments comparing the behavior of *Bacillus* spp. spores across varying environments, conditions, and time periods. During year four, experiments will be conducted with Select Agent strains in the NAU BSL3 facility to generate new data collected from fully virulent strains in order to facilitate comparison of data already collected from non-virulent strains.
- **Determine real world parameters for fate and transport models**
    - o Our experimental work is generating real world data that can be used to parameterize fate and transport models that are being generated by other CAMRA investigators. Values such as natural attenuation rates are being generated and will be transferred to the wider CAMRA group as they become available. Long term experiments of spore survival are ongoing and new experiments using pathogenic strains will be conducted in year 4.
- **Validation of detection methods**
    - o Once a final surrogate is selected, we will generate a real-time PCR assay specific to this strain that can distinguish it from conspecifics and other *Bacillus* species.
- **Deliverables for year 4**
    - o Short-term non-pathogenic surrogate comparisons (liquid and soil).
    - o Long-term fomite and liquid results.
    - o Short-term pathogenic surrogate comparisons (liquid and soil).
    - o Quantitative PCR results of spore survival from short term and long term experiments.
    - o SOPs for soil experiments in BSL3.

Dr. Syed Hashsham's Laboratory (MSU):

- **Genetic Characterization of Highly Touched and Untouched Fomites-Learning Unit 135**
    - o The objective of this task is to assess the microbial diversity from the highly touched and untouched fomites using the 454 GS FLX sequencing. Highly touched and untouched fomites in a university dormitory were sampled by the Influenza Fomite Sampling Project at the University of Michigan.
    - o DNA samples from the highly touched and untouched fomites (1-100 ng) will be amplified by PCR, electrophoresed on a 2% (wt/vol) agarose gel and extracted using Qiagen Gel Extraction Kit. DNA will then be purified using Qiagen PCR Purification Kit. Primers will be designed to target conserved regions surrounding hypervariable regions of relevant genes and amplicons will be used for sequencing. Purified samples will be given to Research Technology Support Facility (RTSF) for the sequencing on 454 of 16S rRNA genes. Data will be analyzed using the 454 Pyrosequencing pipeline available at the RDP-II website http://rdp.cme.msu.edu/.
- **Experimental Evaluation of *Bacillus thuringiensis* Recovered from Fomites-Learning Unit 104**
    - o The objective of this task was to evaluate the parameters that affect the recovery of *B. thuringiensis* at the detection limit (low concentration and large fomite size). The variability in recovery of *B. thuringiensis* (a surrogate for *B. anthracis*) as a function of

fomite type, surface area, sampling time, recovery method and wetting agent will be evaluated.

Nonporous fomites commonly found in indoor environments (acrylic, stainless steel and laminate) with surface areas of 100 cm^2 and 1000 cm^2 will be inoculated with *B. thuringiensis*. A total of 50μl of the sample will be applied to the fomite in a grid formation comprised of fifty 1μL spots. Samples are taken at the initial application time and after the samples are dry. The method of recovery used will be wiped over the surface in horizontal and vertical strokes on the fomite. Methods of recovery evaluated will be the Fellowes Premoistened Surface Cleaning Wipes (48 cm^2), kimwipe (48 cm^2) and cotton swab (4 swabs per fomite). To extract the spores, the recovery method will be vortexed in 5mL of phosphate buffered saline tween-80 (PBST). 1mL of the extraction solution will be used for cultivation.

- **Analysis of Fomite Survival Data-Learning Unit-Learning Unit 708**
    - o The objective of this task is to summarize the factors that influence survival and recovery of microorganisms from fomites. A fomite matrix of data on the survival and recovery of microorganisms on fomites were compiled for Project 1. Further analysis of the data will be carried out in order to summarize the factors that influence the survival and recovery on fomites.
- **Experimental Evaluation of the Environmental Detection Limit for *Bacillus anthracis*-Learning Unit 709**
    - o The objective of this task is to experimentally evaluate the environmental detection limit of *B. anthracis* using the surrogate *B. thuringiensis*. *B. thuringiensis* will be spiked into soil and water samples with various characteristics. Parameters affecting the recovery and detection will be evaluated.

Dr. Mark Nicas' Laboratory (UC Berkeley):

Note: The official start date of the sub-award for UC-Berkeley was September 1, 2005, but grant funds were not available at UC-Berkeley until April 20, 2006. The result is that while Year 4 officially covers the period of September 1, 2008 through August 31, 2009, in practice it covers the period from April 20, 2009 through April 19, 2010.

- **Task 1: Markov chain model**
    - o Draft a manuscript reporting the performance of the Markov chain model in predicting particle deposition in the chamber. We have drafted a manuscript describing the experimental particle deposition data, and a manuscript describing the experimental time-to-mixing and anenometry data. The draft manuscript of the particle deposition data is in second review. In addition, a colleague of Dr. Haas at Drexel University may be able to simulate particle deposition in the test chamber via CFD modeling, such that we can compare the performance of the Markov chain and CFD methods.
- **Task 2: Droplet Spray Exposure**
    - o This is a continuation of a project started in Year 3. A major pathway for person-to-person infection with respiratory tract pathogens (for example, smallpox virus, pneumonic plague *Y. pestis*, influenza A virus) is thought to involve "droplet spray" exposure. For this transmission mode, large particles (primarily of noninspirable diameters) are emitted as projectiles via a cough or sneeze, and strike target facial membranes (the conjunctivae, nostrils, lips) of a person located within three feet of the infector. However, there are no published studies that

have examined exposure potential via this route. We propose to investigate this potential in a straightforward manner. A panel of human subjects will cough at pieces of sample paper (for example, 0.7 m × 0.7 m) which contain outlined features of the eyes, nostrils and lips. The chloride content of the three target sites and of the rest of the paper will be eluted, and the chloride ion concentration will be measured. The proportion of each subject's cough projectile volume that strikes each of the target membranes will be estimated.

A sodium chloride solution in several mL water will be introduced into the mouth for mixing into saliva prior to the cough. The effect of distance between the subjects and the sampling paper will also be determined.

- **Task 3: Choreographed Tests of a Model for the Fomite-Mediated Dose**
  - Based on first principles, a simple model is formulated for the expected number of pathogens transferred onto an individual's fingertip(s) via touching contaminated room surfaces. The inputs are the average pathogen concentration on the surfaces being touched C (# per cm^2), the area of the room surface contacted per touch A (cm^2 per touch), the rate of touching room surfaces H (touch per hour), the transfer efficiency from the touched surface to the finger tip ε_1 (a fraction between 0 and 1), the transfer efficiency from the fingertip back to a touched surface ε_2 (a fraction between 0 and 1), and the duration of the process T (hour). Without regard to pathogen die-off, and assuming no overall change in C due to touching, the number of pathogens on the finger tip at the end of n = H × T touches, denoted D, is:

  Eq. (1)
  $$ D = \varepsilon_1 \times C \times A \times \sum_{i=1}^{n} (1-\varepsilon_2)^{n-i} $$

  If the pathogen concentrations differ between the touched surfaces and are predetermined, the dose algorithm is modified as follows:

  Eq. (2)
  $$ D = \varepsilon_1 \times A \times \sum_{i=1}^{n} C_i \times (1-\varepsilon_2)^{n-i} $$

  The intention is to "choreograph" sequences of touches by one or more individuals to examine the validity of predicting D by Equation (2). A non-pathogen such as a bacteriophage or influenza vaccine strain virus would be used, and the agent would be assayed by a plaque assay (for a phage) and/or quantitative polymerase chain reaction. For example, known numbers of virus would be seeded onto three demarcated areas 1 cm in diameter such that the respective concentrations are C_1, C_2 and C_3. Using the same fingertip, a subject would enact the following sequence: (1) touch the first seeded area; (2) touch two clean areas; (3) touch the second seeded area; (4) touch two clean areas; and (5) touch the third seeded area. The predicted dose on the fingertip is:

  Eq. (3)
  $$ D = \varepsilon_1 \times A \times \left(\left[C_1 \times (1-\varepsilon_2)^4 \right] + \left[C_2 \times (1-\varepsilon_2)^2 \right] + C_3 \right) $$

An important set of choreographed sequences is having a subject touch one or more areas that were previously touched by a different subject with a contaminated fingertip. That type of experiment directly examines the ability of fomite-mediated pathogen transfer between individuals.

As part of this task, a choreographed sequence using an influenza vaccine strain virus would be designed in conjunction with Mr. Ian Spicknall (PhD candidate) and Dr. Joe Eisenberg at the University of Michigan to test Mr. Spicknall's virus dosing model with regard to fomite transfers. As part of the work of CAMRA Group 2, Mr. Spicknall is developing a computer model that explicitly incorporates interactions between individuals including the touching of common surfaces. Any pre-determined sequence of touching common surfaces is simply a choreographed sequence as described here. Thus, a choreographed sequence experiment can be used to investigate the validity of a key part of Mr. Spicknall's model.

- **Task 4: Field Investigation of Influenza Virus in Patient Rooms**
  - The intent is to conduct a pilot study of influenza virus concentrations on surfaces in influenza patient rooms, and on the disposed gloves and respirator filter media of health care workers (HCWs) who attend these influenza in-patients. The study would be conducted at a University of California, San Francisco, hospital in conjunction with Robert Harrison, MD, MPH. Dr. Harrison is a UC-SF faculty member in Occupational and Environmental Medicine, and Chief of the Occupational Hazard Surveillance and Evaluation Program at the California Department of Public Health. At UC-SF, admitted patients with confirmed influenza (A or B) are placed in negative-pressure, single-occupancy rooms. HCWs entering the patient rooms are required to wear disposable gloves and a disposable N95 filtering-facepiece respirator.

    By prior arrangement, the hospital Infection Control Officer would inform Dr. Harrison of the admission of a confirmed influenza patient. An investigator would go on site and spend one or more shifts in the department housing the patient. By prior arrangement, the investigator would collect the gloves and filtering-facepiece respirator that are discarded by a HCW (a nurse) after attending to the influenza patient. At least three sets of gloves/respirators would be collected from one or more HCWs. In addition, swipe samples of nonporous room surfaces close to (e.g. a bedside table) and far from (e.g., the top of a television cabinet) the patient's bed would be collected. In addition, swipe samples of porous surfaces (e.g., bed coverings) would be collected. The swipes would be collected while the patient was out of the room, or might be collected by one a hospital staff member (e.g. Dr. Harrison) while a HCW was attending the patient. Some swipe samples would be collected on surfaces outside the patient's room.

    The environmental samples would be shipped to Dr. Gerba's laboratory at the

University of Arizona. Virus (if present) would be eluted from the fingertip portions of the gloves, from cutout sections of the respirator filters, and from the swipe samples, and assayed by quantitative polymerase chain reaction. Quality control samples (unused gloves and respirators, unused swipe materials) would be included.

The goal is to conduct this environmental virus prevalence monitoring for three to six influenza patients. The exact number depends in large part on the future number of admitted patients, which is uncertain. The expectation is that influenza virus would be found on room surfaces, but perhaps not on respirator filter media, because most virus emitted via coughing is carried in large particles that settle rapidly from room air. However, finding virus on the respirator filter media is suggestive evidence for airborne transmission, and finding influenza virus on glove fingertips is suggestive evidence for fomite-mediated transmission. Moreover, any positive findings would support applying for other funding to conduct a larger study including air sampling inside and outside patient rooms, more extensive swipe sampling inside and outside patient rooms, and nasal swabbing of HCWs. An epidemiological study of influenza incidence among HCWs is not feasible, because the UC-SF hospital actively promotes seasonal vaccination for all its HCWs

- **Note on Human Subjects Review and Approval**
  o At present, Mark Nicas has approval from the UC Berkeley Committee for the Protection of Human Subjects (CPHS # 2008-1-40) for the droplet spray exposure study (proposed Task 2), and has requested an extension for one year. Prior to engaging in any human subject work for the choreographed sequence tests (proposed Task 3) and the field investigation study (proposed Task 4), approval will be obtained from the UC Berkeley CPHS. However, for each of the latter two studies, there is preliminary laboratory work that must be conducted prior to any work involving human subjects.

5. Summary of Research Activities

Researcher Name	Research Activities
Christopher Choi	Evaluating risk assessment
Pedro Romero	Identifying contamination
Ryan Austin	Analyzing water distribution
Amanda Herzog	Analyzing microbial dispersion data Analyzing Availability of DNA Determining Inactivation Investigating surrogates Evaluating detection limit

Charles P. Gerba	Generating transfer data Conducting exposure assessments
David Greenburg	Investigating survival
Mark Nicas	Analyzing risk assessment Modeling Transfer Testing models Measuring exposure Modeling fate and transport
Ryan Sinclair	Analyzing survival

6. Background and prior research:

   Documents read - LU (451):
   The manuscript uses an exposure model (in part run via a Markov chain) that accounts for possible interactions between the pathways of (1) surface-to-hand-to-face contact, (2) respirable particle inhalation, (3) close contact inspirable particle inhalation, and (4) close contact droplet spray exposure. The manuscript explains that the current data on influenza dose delivery and dose-response do not permit identifying a single dominant exposure pathway as some researchers have proposed. In turn, the current planning of nonpharmaceutical interventions for a future avian influenza pandemic should account for all exposure pathways.

   Dr. Mark Nicas and Dr. Rachel Jones. "Relative Contributions of Four Exposure Pathways to Influenza Infection Risk" submitted to Risk Analysis. The manuscript is now in second review.

7. Research Contributions this Year:
   1. Things that are in progress - LU (135):
      Genetic characterization of highly touched and untouched fomites
      Author(s): Amanda Herzog
      When Analyzing microbial dispersion data we wanted to find out the makeup of background bacterial populations at touched and untouched surfaces as illustrated by their 16S rRNA gene.
      Experimental Design:
      Samples will be provided by the Influenza Fomite Sampling Project from the University of Michigan. Samples will be taken from highly touched and untouched fomites in dormitories. DNA samples will be amplified with PCR, run on gel and purified with PCR purification kit. Purified samples will be given to Research Technology Support Facility (RTSF) for the sequencing on 454 of 16S rRNA genes. Primers will be designed to target conserved regions surrounding hypervariable regions of relevant genes, and amplicons will be used for sequencing.

      Things that are in progress - LU (267):
      Survival of viral pathogens on fomites
      Author(s): Ryan Sinclair
      When Analyzing survival we wanted to find out The survival of various pathogens on fomites, evaluate the first-order die-off kinetics as an acceptable statistical model for

survival by the three organisms studied in these investigations.

Things that are in progress - LU (430):
Author(s): Christopher Choi
When Evaluating risk assessment we wanted to find out impact on public health
Experimental Design was as follows:
modeling

Things that are in progress - LU (452):
Transfer efficiencies of bacteriophage and influenza virus
Author(s): Mark Nicas
When Modeling Transfer we wanted to find out Quantify the surface-to-hand and hand-to-surface transfer efficiencies of a bacteriophage and influenza virus..

Things that are in progress - LU (453):
Testing the surface-to-hand dose predictions of exposure model
Author(s): Mark Nicas
When Testing models we wanted to find out
Experimental Design:
Design a human subject experiment that would be used to test the surface-to-hand dose
Predictions of Mr. Spicknalli's exposure model.

Things that are in progress - LU (455):
Ecological assessment of *B. anthracis* strain survival
Author(s): David Greenburg
When Investigating survival we wanted to find out Why *B. anthracis* A group is disseminated worldwide, while other strains are isolated to small regions.
Experimental Design:
Comparing survival of various *B. anthracis* strains under several conditions including liquid, soil and fomite.

Things that are in progress - LU (867):
Modeling axial dispersion in laminar pipe flows
Author(s): Pedro Romero
When Modeling dispersion we wanted to find out Axial dispersion coefficients, E, that are commonly used in the one-dimensional solute transport equation. Conditions are laminar flows.
Experimental Design:
1. Multiple scenarios of flow rates, pipe lengths and injection pulse durations are run 2. Use experimental data as input for computational fluid dynamics (CFD) tools 3. Upon agreement of steps 1 and 2, set up multiple distances at which the concentration profile will be calculated. $C = C(x,t)$, x = distance from inlet, t = time elapsed 4. Use parameter optimization techniques (PDE-constrained optimization) to obtain the targeted CFD-based concencentration curves

Things that are in progress - LU (868):
Contaminant Source Location in water systems with neural network
Author(s): Pedro Romero
When Identifying contamination we wanted to find out To test the capability of artificial neural networks to identify the location and time of a contaminant intrusion in a potable water system

Experimental Design:
1. Define multiple contamination scenarios to establish cause - effect relations (contamination - impacts) 2. Process the pollution data (step 1) in a workable format for neural networks 3. Design neural networks that take the processed data (step 2) as input 4. Train neural networks 5. Validate the capabilities of neural networks to identify location and time of contaminant intrusion with test contamination events

Things that are in progress - LU (869):
Multi-objective Sensor Optimization in Water Distribution Systems
Author(s): Ryan Austin
When Analyzing water distribution we wanted to find out The main objective of the study is to assess the impact that using differing levels of detail in a water quality model has on the design of optimal sensor placement.
Experimental Design:
The unit is analysis of multi-objective sensor placement in water distribution systems. Two sample networks are analyzed to determine optimal sensor placement locations based on multiple criteria. The objectives are based on a previous publication but analysis is done using both EPANET and AZRED as the water quality models.

Things that are in progress - LU (881):
Markov model of particle fate and transport in aircraft cabin
Author(s): Mark Nicas
When Modeling fate and transport we wanted to find out Predict emission of particles from coughs and sneezes in airplane cabin. We assume that Mtb bacilli are emitted during coughing, and consider variability in cough frequency and bacilli concentration in saliva. Use Monte Carlo simulation to estimate exposure variability. Assess dose-response and infection risk.
Experimental Design:
Model exposure using a multizone approach with Markov chain.

Things that are in progress - LU (883):
Tranfersability of organisms from fomite to hand
Author(s): Charles Gerba
When generating Transfer we wanted to find out Determine the degree of expsoure to organisms by contact with fomites.
Experimental Design:
Measure the percent tranfer of surrogates from various types of fomites from the fomite to the hand (skin). Test organisms include coliphage MS-2, E. coli, Staph. aureus and Bacillus thurogenensis spores.

Things that are in progress - LU (885):
Review of transfer of orgnisms from fomites to human skin
Author(s): Charles Gerba
When conducting exposure we wanted to find out The peracentage transfer of organisms from fomites to the human skin
Experimental Design:
REview the literature and analysis the data for development of transfer effeciciencies for different environments

2.

Things that are in progress - LU (104):

Evaluation *B. thuringiensis* recovered from fomites-cultivation

Author(s): Amanda Herzog

When Evaluating detection limit we wanted to find out the method and parameter which results in a high recovery at the detection limit (low concentration/large fomite surface area). .

Experimental Design :

This task involves an experimental evaluation of the detection limit of cultivatable method using *B. thuringiensis* recovered from various fomites. Fomites of interest include plastic, laminar, and stainless steel with surface areas of 0.01 m2, 0.1 m2. *B. thuringiensis* will be serial diluted in an application medium of water. A total of 50Âµl of the sample will be applied to the fomite in a grid formation comprised of fifty 1ÂµL spots. The method of recovery used will be wiped over the surface in horizontal and vertical strokes on the fomite. Methods of recovery evaluated are the Fellowes Premoistened Surface Cleaning Wipes (48cm2), kimwipe (48cm2) and cotton swab (4 swabs per fomite). Samples are taken at the initial application time and after the samples are dry. In addition humidity and temperature will be monitored. Prewetting will be used before recovering a dry sample to increase recovery, 200ÂµL of TSB is distributed uniformly using a spreader (the surface and spreader are wiped). 1mL of the extraction solution will be used for cultivation.

Contribution:

We showed the variability of *B. thuringiensis* recovery as a function of surface type, surface area, recovery time, recovery method and wetting agent.

Results:

At time zero, acrylic resulted in a higher average recovery (73%) than laminate (56%) and stainless steel (54%). There was no significant diference between surface area (1000 cm2 vs 100 cm2) and recovery methods (wipe, kimwipe, and cotton swab) at time zero. When *B. thuringensis* was dry on the surface (90 min) there was a 15% difference in average recovery between 100 cm2 vs 1000cm2. A 45% decrease in average recovery from samples recovered at 90 mins (dry) compared to those recovered at 0 min. However, when using TSB as a wetting agent there was a 15% increase in average recovery for the dry samples.

Things that are in progress - LU (881) and Things that I have completed - LU (882):
Markov model of particle fate and transport in aircraft cabin

Author(s): Mark Nicas

When Modeling fate and transport we wanted to find out Predict emission of particles from coughs and sneezes in airplane cabin. We assume that Mtb bacilli are emitted during coughing, and consider variability in cough frequency and bacilli concentration in saliva. Use Monte Carlo simulation to estimate exposure variability. Assess dose-response and infection risk.

Experimental Design was as follows:

Model exposure using a multizone approach with Markov chain.

Contribution:

Exposure to particles emitted from coughs and sneezes was predicted for passengers in eight rows of the Boeing 767-300 aircraft. Exposures were higher towards the aft of source and near the windows.

Results:

Attached article describe simulations, distributions, and the spatial arrangement of infection risk to individuals seated in each zone.

3. Advances made in unit - LUs (731,135)

Things that are in progress - LU (731) and Things that I have completed - LU (135):

Initially Analyzing Availability of DNA we wanted to find out the make up of background bacterial populations at touched and untouched surfaces as illustrated by their 16S rRNA gene.
Author(s): Amanda Herzog
The original Experimental Design was as follows:
the makeup of background bacterial populations at touched and untouched surfaces as illustrated by their 16S rRNA gene.
We are currently trying to find out the makeup of background bacterial populations at touched and untouched surfaces as illustrated by their 16S rRNA gene.
The current Experimental Design is as follows:
Samples will be provided by the Influenza Fomite Sampling Project from the University of Michigan. Samples will be taken from highly touched and untouched fomites in dormitories. DNA samples will be amplified with PCR, run on gel and purified with PCR purification kit. Samples will be processed to extract DNA. DNA will be evaluated for its quality and quantity. 16S rRNA genes will be amplified by using universal primers with 454 associated tags. Primers will be designed to target conserved regions surrounding hypervariable regions of relevant genes, and amplicons will be used for sequencing. Amplified 16S rRAN genes will be purified. Purified 16S genes will be given to Research Technology Support Facility (RTSF) for the sequencing on 454 of 16S rRNA genes.

Loss due to recovery vs loss due to decreased infectivity of P22 - LUs (799,128):
Things that are in progress - LU (799)
Author(s): Amanda Herzog, Alok Pandy
Initially Determining Inactivation we wanted to find out to distinguish between loss due to recovery from loss due to decreased infectivity of P22 on fomites
The original Experimental Design was as follows:
to distinguish between loss due to recovery from loss due to decreased infectivity of P22 on fomites
We are currently trying to find out To distinguish between loss due to recovery from loss due to decreased infectivity of P22 on fomites
The current Experimental Design is as follows:
P22 is grown and serial diluted to various concentrations. For this modified method, P22 drops applied directly on the 100mm X 15mm plastic petri- dish and left to dry. After the drops were completely dried, 1 ml of TSB added over the dried drops and properly spread using a plastic bacteria spreader. This solution is now as the P22 sample overlaid with mixture of 3ml bacto agar, 1ml TSB and 500ÂμL log phase-host cell culture with proper mixing and incubated in inverted position for 18-24 hr at 370C. Plaques were scored for the number of active P22 particles.

Quantum dots as surrogates for microorganisms LUs (800,505)
Things that are in progress LU (800)
Author(s): Amanda Herzog
and Things that I have progress LU (505)

Author(s): Alok Pandey

Initially Investigating surrogates we wanted to find out what are the best surrogates for microorganisms

The original Experimental Design was as follows:

what are the best surrogates for microorganisms

We are currently trying to find out Suitability of quantum dots as a surrogate for microorganisms.

The current Experimental Design is as follows:

The work on evaluation of quantum dots as surrogate involves identification of characteristics of all types of quantum dots and theoretical evaluation of QDs for use as surrogate followed by an experimental validation of its usefulness. Literature review suggests that it has good potential but its use as surrogate will require further evaluation and development. Major criteria selected for a suitable surrogate are size, detection limit, cost, measurement techniques and toxicity.

Quantum dots as surrogates for microorganisms LUs (800,506)

Things that are in progress LU (800)

Author(s): Amanda Herzog

and Things that I have progress LU (506)

Author(s): Alok Pandey

Initially Investigating surrogates we wanted to find out quantum dots used as surrogates are genotoxic (at what level to human population handling it) or not

The original Experimental Design was as follows:

quantum dots used as surrogates are genotoxic (at what level to human population handling it) or not

We are currently trying to find out Suitability of quantum dots as a surrogate for microorganisms.

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Quantum dots as surrogates for microorganisms LUs (800,507)

Things that are in progress LU (800)

Author(s): Amanda Herzog

and Things that I have progress LU (507)

Author(s): Alok Pandey

Initially Investigating surrogates we wanted to find out Suitability of quantum dots as a surrogate for microorganisms.

The original Experimental Design was as follows:

Suitability of quantum dots as a surrogate for microorganisms.

We are currently trying to find out Suitability of quantum dots as a surrogate for microorganisms.

The current Experimental Design is as follows:

The work on evaluation of quantum dots as surrogate involves identification of characteristics of all types of quantum dots and theoretical evaluation of QDs for use as surrogate followed by an experimental validation of its usefulness. Literature review suggests that it has good potential but its use as surrogate will require further evaluation

and development. Major criteria selected for a suitable surrogate are size, detection limit, cost, measurement techniques and toxicity.

Experimental verification of axial dispersion in laminar flows LUs (872,867)
Things that are in progress LU (872)
Author(s): Pedro Romero
and Things that I have progress LU (867)
Author(s): Pedro Romero
Initially Validating models we wanted to find out Axial dispersion coefficients, E, that are commonly used in the one-dimensional solute transport equation. Conditions are laminar flows.
The original Experimental Design was as follows:
Axial dispersion coefficients, E, that are commonly used in the one-dimensional solute transport equation. Conditions are laminar flows.
We are currently trying to find out Experimental quantification of axial dispersion effects in single pipes of pressurized distribution systems
The current Experimental Design is as follows:
1. Condition municipal tap water to reduce conductivity through filters, reverse osmosis and de-ionizer units 2. Pump conditioned water to main pipe section 3. Inject salt tracer with a smaller pump into the main water source 4. Measure and record conductivity at upstream and downstream locations 5. Determine salinity concentrations based on conductivity readings 6. Carry out steps 1 thru 6 under multiple scenarios of flow rates, pipe lengths and injection durations

Single-objective sensor optimization in potable water systems LUs (873,869)
Things that are in progress LU (873)
Author(s): Pedro Romero
and Things that I have progress LU (869)
Author(s): Ryan Austin
Initially Identifying contamination we wanted to find out The main objective of the study is to assess the impact that using differing levels of detail in a water quality model has on the design of optimal sensor placement.
The original Experimental Design was as follows:
The main objective of the study is to assess the impact that using differing levels of detail in a water quality model has on the design of optimal sensor placement.
We are currently trying to find out Improved water quality models produce more representative input data for optimal sensor placements
The current Experimental Design is as follows:
1. Define multiple contamination scenarios 2. Simulate the contamination scenarios with EPANET 3. Summarize contamination impacts in pollution matrix 4. Run single-objective optimization formulation to minimize the number of water quality monitoring units for full detection coverage 5. Carry out steps 1 thru 4 with improved water quality models 6. Evaluate the impact of improvements in water quality modeling on sensor placements

Developments in experiments on droplet spray exposure as a pote LUs (880,142)
Things that are in progress LU (880)
Author(s): Mark Nicas
and Things that I have progress LU (142)
Author(s): Mark Nicas
Initially Measuring exposure we wanted to find out The fraction of cough particle volume

that strikes the eyes, nostrils, and lips of a person in close contact

The original Experimental Design was as follows:

The fraction of cough particle volume that strikes the eyes, nostrils, and lips of a person in close contact

We are currently trying to find out The fraction of cough particle volume that strikes the eyes, nostrils, and lips of a person in close contact

The current Experimental Design is as follows:

Introduce a small volume of saline solution in a subject. We have purchased a chloride ion electrode better than the previous two. We obtained calibration curves and completed elution efficiency experiment.

4. Loss due to recovery vs loss due to decreased infectivity of P22 LUs (131,799)

Things that are in progress LU (799)

Author(s): Amanda Herzog

and Things that I have completed LU (131)

Author(s): Alok Pandey

Once we learned:

Low recovery in P22-fomite experiments is because of inactivation of the virus particles after drying on the surface

This result led us to the following research question Determining Inactivation we wanted to find out To distinguish between loss due to recovery from loss due to decreased infectivity of P22 on fomites

The current Experimental Design is as follows:

P22 is grown and serial diluted to various concentrations. For this modified method, P22 drops applied directly on the 100mm X 15mm plastic petri- dish and left to dry. After the drops were completely dried, 1 ml of TSB added over the dried drops and properly spread using a plastic bacteria spreader. This solution is now as the P22 sample overlaid with mixture of 3ml bacto agar, 1ml TSB and 500ÂμL log phase-host cell culture with proper mixing and incubated in inverted position for 18-24 hr at 370C. Plaques were scored for the number of active P22 particles.

8. Outputs:
   1. Students Supported:
      Amanda Herzog, supervisor: Dr. Syed Hashsham.
      Ryan Austin, supervisor: Dr. Christopher Choi
      Pedro Romero, supervisor: Dr. Christopher Choi
      Surakshya Dhakal, supervisor: Dr. Mark Nicas

   2. Students Graduated:
      Ms. Surakshya Dhakal will be receiving her MS degree in Spring 2009
      Ms. Surakshya Dhakal, who participated in conducting the time-to-mixing experiments while funded by the UC-Berkeley CAMRA subaward, will be receiving her MS degree in Spring 2009. The candidate title for her thesis is "Exploring the Relationships between Time-to-Mixing, Turbulence Intensity, and the Turbulent Diffusion Coefficient." Supervised by Professor Mark Nicas.

   3. Publications:
      B. anthracis Detection Limit Paper
      Herzog AB, McLennan SD, Pandey AK, Gerba CP, Haas CN, Rose JB, Hashsham SA. 2009. Implications of Limits of Detection of Various Methods for *Bacillus anthracis* in Computing Risk to Human Health. Applied Environmental Microbiology. 75:6331-6339.

Demonstration of the use of the bacteriophage MS-2 to study dispersion of viruses in distribution systems and data that can be used to define axial dispersion
Sinclair, R. *et al.* 2009. Assessment of MS-2 phage and salt tracers to characterize axial dispersion in water distribution systems. Journal of Environmental Science and Health. 44: 963-971.

Surakshya Dhakal`s MS Thesis
S. Dhakal, "A Study to Improve the Markov Chain Indoor Air Model Parameter to Enhance Its Use in Public Health Exposure Assessment" M.S. Thesis, University of California, Berkeley, 2009.

Modeling TB Bacilli Transport and Fate in an Airplane Cabin with the Markov Chain Model
Rachael Jones, et al. 2009. Characterizing the risk of infection from *Mycobacterium tuberculosis* in commercial passenger aircraft using quantitative microbial risk assessment. Risk Analysis 29, page 355.

Airborne Particle Transport and Fate Experimental Data
Rachael Jones and Mark Nicas.(2009) Experimental Determination of supermicrometer particle fate subsequent to a point release within a room under natural and forced mixing.Aerosol Science and Technology. 43: 921-938.

Relating Turbulence Intensity and Time-to-Mixing
Draft of a manuscript titled "Mixing of a point source contaminant within a room and realtionship with turbulenece parameters" by Rachael Jones. *et al.*

4. Patents:

5. Presentations:
    CAMRA All PI Meeting
    Amanda Herzog presented at the CAMRA All PI Meeting October 20-22, 2009. Title: Validation of Detection Methods

    Modeling virus risks
    Presented at Risk Analysis of Complex Systems for National Security Applications. Santa Fe, NM April 7, 2009.

6. Organization of workshops:
7. Participation in workshops:
    Instructor at the 4th QMRA Workshop
    Charles P. Gerba served as an instructor for the workshop
8. Case studies
9. Algorithms developed:

10. Human Resource Development:
11. Funds Leveraged:
12. Other:
    M.S. Student Award
    Amanda Herzog received "Outstanding M.S. Student Award in Environmental

Engineering" for the 2008-2009 academic year on May 8, 2009. University of California Berkeley

Interview with Canadian Discovery Channel
Mark Nicas appeared in a television interview about the role of droplet spray exposure in influenza transmission.

9. Outcomes:
Unit 135: Risk assessors and modelers will have better knowledge about genetic characteristics of influenza.

Unit 267: Development of a "cookbook" of inactivation coefficients for survival of viruses on fomites. A publication detailing the experimental results.

Unit 430: QMRA and consequence modeling.

Unit 452: The experimental data would serve as inputs for an influenza transmission model being developed by Ian Spicknall (with the input of Drs. Eisenberg, Koopman and Nicas) at University of Michigan.

Unit 455: Better understanding of *B anthracis* ecology.

Unit 731: Occurrence data for bacterial populations and presence of bacterial pathogens.

Unit 799: PFUs scored from this method will show the number of active P22 particles as there is no loss due to recovery method involved.

Unit 800: Suitable QD as surrogate for microorganisms on the basis of size, detection limit, cost, measurement techniques and toxicity will be found theoretically. If it fulfills these criteria, it will be used for further experimental validation.

Unit 842: First responders responsible from recovering bacterial spores from fomites will have better knowledge.

Unit 867: An improved 1D-ADR equation widely used in modeling water distribution systems.

Unit 868: A general guideline for application of neural networks in the field of water security.

Unit 869: Better knowledge and methods for sensor placement in water distribution systems.

Unit 872: Experimental baseline to develop axial dispersion coefficients.

Unit 873: Overall improvement in water security modeling tools.

Unit 883: The results can be used in exposure models to determine the degree of expsoure from contact with fomites. The results may also lead to the development of surface materials that could reduce the transfer of organisms from the fomite to the huan skin.

Unit 885: Values of percent transfer that could be used in exposure models.

10. Integration with other projects:
An association was created between Unit 469, authored by Patrick Gurian (Project IV, Drexel University) and Unit 478, authored by Mark Nicas (Project I, U of California Berkeley).

An association was created between Unit 484, authored by Rachael Jones (Project I, U of California Berkeley) and Unit 481, authored by Shamia Hoque (Project III, Drexel University).

An association was created between Unit 481, authored by Shamia Hoque (Project III, Drexel University) and Unit 487, authored by Christopher Choi (Project I, U of Arizona).

An association was created between Unit 579, authored by David David Greenburg (Project I, Northern Arizona U) and Unit 490, authored by Christopher Choi (Project I, U of Arizona).

An association was created between Unit 476, authored by Mark Nicas (Project I, U of California Berkeley) and Unit 519, authored by Ian Spicknall (Project II, U of Michigan).

An association was created between Unit 58, authored by Rosina Weber (Project V, Drexel University) and Unit 877, authored by Christopher Choi (Project I, U of Arizona).

11. Anticipated Technical Results and Developments

CAMRA Report for Year IV (September 15, 2008 to September 14, 2009) for Project II

1. Project II
2. Investigators: Joe Eisenberg, James Koopman, Josep Pujol, Ian Spicknall, Sheng Li, Nottasorn Plipat, Bryan Mayer, Scott McLennan , Jijun Zhao
3. Project Goals:
Transmission Model Development including (including dynamics of environmental contamination, dose-response, and behavior, as well as intra- and inter-venue transmission of pathogens).
4. Tasks for Year IV (September 15, 2008 to September 14, 2009):

The tasks for the Year IV come out of our four main areas of research: developing a framework for analysis of environmental infection transmission systems (EITS); developing physiologically based dose-response models (effects of exposure dynamics in dose response relationships); determining dominant modes of transmission for Influenza; and determining the role of the environment in methicillin resistant *Staphlococcus aureaus* (MRSA) infection transmission. Below is a detailed description of our 4 main tasks for Year 4.

First, we plan to complete the development of our framework for environmentally mediated transmission dynamics. This framework broadens our previous work that had incorporated the environmental dynamics of pathogens in water to pathogen contamination of fomites and air. We plan to publish our initial work that considers a single homogeneous environment (Note: This manuscript was just accepted in the American Journal of Epidemiology; see LUs). We will then extend that to models with venue structure that incorporates human movement and also to models that incorporate multiple venues.

Second, we plan to publish our initial cumulative dose-response model that we developed during Years 2 and 3 (Note: this manuscript was just accepted in PLoS Computational Biology; see

LU). We plan to use this model to analyze an observational data set that monitored deaths of monkeys to continuously varying anthrax exposure. We also plan to begin an collaboration with Carol Bolin at MSU on conducting experiments in a mouse/tularemia model system that came be used to validate our conceptual dose-response model as well as parameterize the model. We will also begin dialog with others at EPA for similar collaborations.

Third, we plan to develop an individual based model of influenza transmission to examine the dominant models of transmission. We will do this by first contextualizing other similar models in the literature (namely Atkison and Wien, and Nicas) so that we can articulate how and why conclusions may differ in the context of uncertainty and sensitivity of the outcome (which model of transmission is dominant) on parameter values. We plan to publish this result and then extend the model as a risk assessment tool in collaboration with Patrick Gurian.

Fourth, we plan to apply the modeling concepts that we have learned in the above work to examine the role of the environment in methicillin resistant *Staphlococcus aureaus* (MRSA) infection transmission surgical intensive care units (SICU). This work will be in collaboration with the University of Michigan hospital.

5. Research Activities

Researcher Name	Research Activity
Ian Spicknall	Modeling transmission Developing case studies
Jijun Zhao	Modeling transmission

6. Background and prior research

7. Research Contributions this Year:
    1. Regions of influenza transmission mode dominance in parameter space LUs (335,738)
        Things that are in progress LU (335)
        Author(s): Ian Spicknall
        and Things that I have completed LU (738)
        Author(s): Ian Spicknall
        When Modeling transmission we wanted to find out We are investigating how specific parameters related to biology, behavior and venue specific features affect transmission mode dominance. In addition, we are explaining how previous work of Atkinson and Wein (2007) and Nicas and Jones (2009) arrived at different conclusions from each other and to some degree different conclusions from us.
        Experimental Design:
        We developed a mechanistic model of influenza transmission through the environment, in which there is explicit modeling of environmental processes related to aerosol and contact mediated infection. We conducted a thorough literature search to inform upper and lower parameter value constraints. We then draw a latin hypercube sample considered as our entire parameter space. We then divide this entire parameter space into different regions where different modes of transmison dominate over others.
        Contribution:
        Host density, relative infectivity are both important parameters determining whether there

is high or low transmission via the droplet and respiratory route. For the contact route, the self-inoculation rate and infectivity are the most important parameters.

Results:

Both mode-specific and total R0 appear to be highly sensitive to parameter variability. Given our constrained parameter space, the inspiratory mode is largely negligible, while the respiratory, contact-mediated, and droplet modes all have multiple regions where they alone are sufficient to cause pandemic transmission.

8. Outputs:
    1. Students Supported:
       Ian Spicknall
       Bryan Mayer
       Jijun Zhao
       Sheng Li
       Nottasorn Pilat
    2. Students Graduated:
    3. Publications:
    4. Patents:
    5. Presentations:
    6. Organization of workshops:
    7. Participation in workshops:
    8. Case studies algorithms developed:
    9. Algorithms developed:
    10. Human Resource Development:
    11. Funds Leveraged:

9. Outcomes:
   Unit 738: Influenza may be transmitted by different modes in different contexts. This has implications for effective intervention design and implementation.

   Unit 924: 1) Parameter ranges that will yield specific system behaviors. 2) Analysis measures for relative importance of routes when related parameter ranges are known. 3) Analysis measures for relative contributions of routes under different environmental settings. 4) Results that might be applied for helping decision making.

10. Integration with other projects:
    An association was created between Unit 372, authored by Sheng Li (Project II, U of Michigan) and Unit 426, authored by Scott McLennan (Project IV, Michigan State U).

    An association was created between Unit 476, authored by Mark Nicas (Project I, U of California Berkeley) and Unit 519, authored by Ian Spicknall (Project II, U of Michigan).

    An association was created between Unit 748, authored by Ian Spicknall (Project II, U of Michigan) and Unit 762, authored by Patrick Gurian (Project IV, Drexel University).

11. Anticipated Technical Results and Developments:

CAMRA Report for Year IV (September 15, 2008 to September 14, 2009) for Project III

1. Project III
2. Investigators: Charles N. Haas, Mark Weir, Tim Bartrand, Carole Bolin, Sushil Tamrakar, Sharon Nappier , Yin Huang , Toru Watanabe, Shamia Hoque
3. Project Goals: Comprehensive review of experimental dose response data available from open literature.
Development and validation of dose response models for bioterrorism agents and other biological agents of concern.
Experimental development of dose response data for infection and death related to oral challenge with *Francisella tularensis* in mice.

4. Tasks for Year IV (September 15, 2008 to September 14, 2009):

   A mechanistic dose response model will be developed for multiple routes of exposure, and interspecies relationships.

   Mechanistic incorporation of the post exposure time dependence of dose response models, for multiple pathogens, including *Bacillus anthracis*, *Yersinia pestis* and *Francisella tularensis.*

   Working with Project II at the University of Michigan to on coupling dose-response-time models to population models.

   The Influenza alert being completed in the current funding year will be expanded to a CAMRA-wide scenario analysis, such as a national epidemic or replication of the H1N1 outbreak of Spring 2009.

   Tularemia multiple exposure trials are ongoing at Michigan State University (MSU). The dose response relationships will be modeled when these data become available.

   The growth data recorded in the MSU data will allow for kinetics models to be developed of tularemia growth in the host.

   Viral encephalitis viruses and age dependency of these viruses where modeled in the later part of the current funding year. Growth kinetics models will be developed as well since it seems that growth rate data is available for such model construction.

5. Research Activities

Researcher Name	Research Activity
Mark H. Weir	Gathering data Developing advanced model framework Modeling physiology and kinetics Modeling dose response Analyzing dose response model

Sushil Tamrakar	Gathering data Assessing behavior Modeling dose response
Sharon Nappier	Modeling dose response Gathering data Analyzing dose response model
Yin Huang	Gathering data Modeling dose response Analyzing dose response Validating dose response
Charles N. Haas	Gathering data
Toru Watanabe	Modeling dose response Analyzing dose response model

6. Background and prior research:

Things I have read - LU (662):
The data required to include particle size into a dose response assessment was gathered from the references in this learning unit. This information was used to develop the dose response assessment that is shown in the document attached to the Accomplishment Unit LU (287).

Druett, H.A., Henderson, D.W. et al. 1953. Studies on Respiratory Infection I. The Influence of Particle Size on Respiratory Infection with Anthrax Spores. Journal of Hygiene. 51: 359-371.

Altboum, Z., Gozes, Y., et al. 2002. Postexposure Prophylaxis against Anthrax: Evaluation of Various Treatment Regimens in Intranasally Infected Guinea Pigs. Infection and Immunity. 70(1): 6231-6241.

Things I have read - LU (444):
Rickettsia prowazekii normally grows within Endothelial cells in vivo. Rickettsiae preferentially infects endothelial cells in vivo of the route of infection of the host. Louse feces enter host tissue through a hole created during a louse blood mea.
Walker, T. S. 1984. Rickettsial interactions with human endothelial cells in vitro: adherence and entry. Infection and Immunity. 44(2): 205-210.

Things I have read - LU (640):

The pathogenecity, manifestation and occuerence of the diseases.
Azad, A. F. 1990. Epidemiology of Murine Typhus. Annual Review of Entomology. 35(1): 553-570.

Azad, A. F. 2007. Pathogenic Rickettsiae as Bioterrorism Agents. Clinical Infectious Diseases. 45(s1): S52-S55.

Bechah, Y., C. Capo, G. E. Grau, D. Raoult and J.-L. Mege 2007. A murine model of infection with Rickettsia prowazekii: implications for pathogenesis of epidemic typhus. Microbes and Infection. 9(7): 898-906.

Bechah, Y., C. Capo, J.-L. Mege and D. Raoult 2008. Rickettsial diseases: from Rickettsia arthropod relationships to pathophysiology and animal models. Future Microbiology. 3(2): 223-236.

DuPont, H. L., R. B. Hornick, A. T. Dawkins, G. G. Heiner, I. B. Fabrikant, C. L. J. Wisseman and T. E. Woodward 1973. Rocky Mountain spotted fever: a comparative study of the active immunity induced by inactivated and viable pathogenic Rickettsia rickettsii. The Journal of Infectious Diseases. 128(3): 340-344.

Everritt, M. G., P. N. Bhatt and J. P. Fox 1954. Infection of Man with Avirulent Rickettsia of Epidemic Typhus. American Journal of Hygiene. 59(1): 60-73.

Gonder, J. C., R. H. Kenyon and C. E. Pedersen, Jr. 1979. Evaluation of a killed Rocky Mountain spotted fever vaccine in cynomolgus monkeys. Journal of Clinical Microbiology. 10(5): 719-723.

Hackstadt, T. 1996. The biology of rickettsiae. Infectious Agents and Disease. 5(3): 127-143.

Houhamdi, P. E. Fournier, R. Fang and D. Raoult. 2003. An Experimental Model of Human Body Louse Infection with Rickettsia typhi. Annal of the New York Academy of Sciences. 990(Rickettsiology: Present and Future Directions): 617-627.

Keenan, K. P., W. C. Buhles Jr, D. L. Huxsoll and R. G. Williams. 1977. Studies on the pathogenesis of Rickettsia rickettsii in the dog: clinical and clinicopathologic changes of experimental infection. American Journal of Veterinary Research. 38(6): 851-856. 11.

Kenyon, R. H., R. A. Kishimoto and W. C. Hall. 1979. Exposure of guinea pigs to Rickettsia rickettsii by aerosol, nasal, conjunctival, gastric, and subcutaneous routes and protection afforded by an experimental vaccine. Infection and Immunity. 25(2): 580-582.

Lacz, N. L., R. A. Schwartz and R. Kapila. 2006. Rocky Mountain spotted fever. Journal of the European Academy of Dermatology and Venereology. 20(4): 411-417.

Mooty, M. and L. I. Lutwick. 2009. Epidemic Typhus Fever. Beyond Anthrax. L. I. Lutwick and S. M. Lutwick, Humana Press: 1-22.

Parola, P., C. D. Paddock and D. Raoult. 2005. Tick-Borne Rickettsioses around the World: Emerging Diseases Challenging Old Concepts. Clinical Microbiology Reviews. 18(4): 719-756.

Raoult, D. and V. Roux. 1997. Rickettsioses as paradigms of new or emerging infectious diseases. Clinical Microbiology Reviews. 10(4): 694-719.

Raoult, D., P. J. Weiller, A. Chagnon, H. Chaudet, H. Gallais and P. Casanova. 1986. Mediterranean Spotted Fever: Clinical, Laboratory and Epidemiological Features of 199 Cases. American Journal of Tropical Medicine and Hygiene. 35(4): 845-850.

Raoult, D., T. Woodward and J. S. Dumler. 2004. The history of epidemic typhus. Infectious Disease Clinics of North America. 18(1): 127-140.

Reynolds, M. G., J. S. Krebs, J. A. Comer, J. W. Sumner, T. C. Rushton, C. E. Lopez, W. L. Nicholson, J. A. Rooney, S. E. Lance-Parker, J. H. McQuiston, C. D. Paddock and J. E. Childs. 2003. Flying squirrel-associated typhus, United States. Emerging Infectious Diseases. 9(10): 1341-1343.

Saslaw, S. and H. N. Carlisle. 1966. Aerosol infection of monkeys with Rickettsia rickettsii. Bacterological Riviews. 30(3): 636-645.

Walker, D. H. 1989. Rocky Mountain spotted fever: a disease in need of microbiological concern. Clinical Microbiology Reviews. 2(3): 227-240.

Walker, D. H. and D. B. Fishbein. 1991. Epidemiology of rickettsial diseases. European Journal of Epidemiology. 7(3): 237-245.

Things I have read - LU (659):
The authors demonstrated that the infection probability of hamsters ingesting scrapie agents is highest when all the infectivity is given at once, and decreases as the interval between successive challenges increases.
H. Diringer, J. roehmel and M. Beekes. 1998. Effect of repeated oral infection of hamsters with scrapie. Journal of General Virology. 79(3): 609-612.

Things I have read - LU (741):
The authors demonstrated that the infection probability of mice receiving repeated intraperitoneal injections of prion doses is higher than that of single dosing.
C. Jacquemot, C. Cuche, D. Dormont and F. Lazarini. 2005. High Incidence of Scrapie Induced by Repeated Injections of Subinfectious Prion Doses. Journal of Virology. 8904-8908.

7. Research Contributions this Year:

1. Dose-response model for influenza A virus Things that are in progress - LU (294):
   Author(s): Toru Watanabe
   When Modeling dose response model we wanted to find out 1) Dose-response model for influenza A virus. 2) Relationship between taxonomy of influenza A virus and its infectivity (or virulence).
   Experimental Design:
   1) Collecting datasets for human infection with various strains of influenza A virus. 2) Fitting dose-response models to the datasets. 3) Evaluating infectivity (or virulence) of each virus strain and comparing them focusing on the taxonomy of influenza A virus.

   Dose-Response Model for *Coxiella burnetii* (Q fever) Things that are in progress - LU (311):
   Author(s): Sushil Tamrakar

When Developing dose response model we wanted to find out to develop dose-response model for Q fever
Experimental Design:
1- Mining the usable data, 2- Test for dose-response trend 3- Develop dose-response models 4- Evaluate best fit model 5- Low dose extrapolation.

Equine Encephalitis Dose Response Things that are in progress - LU (386):
Author(s): Charles N. Haas
When Gathering data we wanted to find out exponential or beta-poisson models provide adequate fits to these data
Experimental Design:
literature review, extraction of data for use by modeling

Equine Encephalitis Virus - Dose Response Models Things that are in progress - LU (437):
Author(s): Sharon Nappier
When Analyzing dose response model we wanted to find out The dose of equine encephalitis required to elicit a response in mice.
Experimental Design:
Dose response data was found in the peer-reviewed literature and fit with three dose resposne models. Data was also evaluated with a model modified with an age-dependency parameter. Data was evaluated from three routes of exposure: intracranial, intraperitoneal, and subcutaneous.

Dissertation: Incorporating time to response into dose-response Things that are in progress - LU (445):
Author(s): Yin Huang
When Developing dose response model we wanted to find out Time-dose-response model could provide significantly acceptable fit to the human morbidity dose-response data and its modified form could be fitted with the response data of multiple-dose challenges in order to quantify the effect of different dosing schedules.
Experimental Design:
This is my dissertation work. The open literature will be searched for human time to response data and multiple challenges data. For available human morbidity dose-response data with the time to symptoms onset and the time to recovery, the initial appearance of symptoms will be chosen as the end point and the proposed time-dose-response model will be fitted with these human data using MLE method. For multiple challenge data, the probability of response caused by different dosing schedules will be compared by using more complex time-dose-response models.

A QMRA Model for Rickettsial Diseases Things that are in progress - LU (655):
Author(s): Sushil Tamrakar
When Analyzing dose response model we wanted to find out It is hypothesized that there is definite relationship between route of infection and the outcome of diseases, host animals and response and strain of pathogen and severity of disease. We will develop a correction factor that will transform one route of infection to another route.
Experimental Design:
Starting from the classical dose-response model, we will try to develop modified model that incorporate inter-route correction factor/s and interspecies correction factors.

2. Equine Encephalitis Virus - Dose Response Models - LUs (437,446):
   Things that are in progress - LU (437)
   Author(s): Sharon Nappier
   and Things that I have completed - LU (446)
   Author(s): Sharon Nappier
   When Analyzing dose response model we wanted to find out The dose of equine encephalitis required to elicit a response in mice.
   Experimental Design:
   Dose response data was found in the peer-reviewed literature and fit with three dose resposne models. Data was also evaluated with a model modified with an age-dependency parameter. Data was evaluated from three routes of exposure: intracranial, intraperitoneal, and subcutaneous.
   Contribution:
   Venezeualan, Western, and Equine encephalitis viruses could be pooled by the intracranial route using a modified beta-Poisson dose response model with an age-dependency parameter.
   Results:
   Dose-response relationships for Venezuelan, Western, and Eastern equine encephalitis viruses by inoculation route and host age were created.

   Dose-Response Model for Lassa Virus - LUs (304,646):
   Things that are in progress - LU (304)
   Author(s): Sushil Tamrakar
   and Things that I have completed - LU (646)
   Author(s): Sushil Tamrakar
   When Developing dose response we wanted to find out Estimation of risk on the beasis pf dose-response model
   Experimental Design:
   1- Mining the usable data, 2- Test for dose-response trend 3- Develop dose-response models 4- Evaluate best fit model 5- Low dose extrapolation.
   Contribution:
   Usable data set
   Results:
   The suable data sets were tested for the test of trend and proceded for furhther analysis.

   Dose-Response Model for *Burkholdria pseudomallei* (Melioidosis) - LUs (310, 649):
   Things that are in progress - LU (310)
   Author(s): Sushil Tamrakar
   and Things that I have completed - LU (649)
   Author(s): Sushil Tamrakar
   When Developing dose response model we wanted to find out Trying to develop Dose-Response Model for the bactearia Burkholderia pseudomallei
   Experimental Design:
   1- Mining the usable data, 2- Test for dose-response trend -Cochran-Armitage Test. 3- Develop dose-response models 4- Evaluate best fit model 5- Low dose extrapolation.
   Contribution:
   best fit model

   Physiologically Based Pathogen Transport and Kinetics Models - LUs (211, 756):
   Things that are in progress - LU (211)
   Author(s): Mark Weir

and Things that I have completed - LU (756)

Author(s): Mark Weir

When Developing dose response model we wanted to find out What the effective dose (true disease causing dose) is for inhaled pathogens. Whether bulk fluid and intracellular transport can be modeled in a engineering framework (complex media analysis, two phase mass transfer and laminar bulk fluid flow). Whether the effective dose will improve the accuracy of the estimation of risk for disease from *B. anthracis*.

Experimental Design:

The dose inhaled in a malicious or natural pathogen release is not necessarily the dose that is causing the disease. There exist a number of mechanisms that allow for the dose to be reduced or in some cases with rapid multiplication increase. By examining the pathogenesis of *Bacillus anthracis* (*B. anthracis*) it can be seen that these pathogens have defined routes of infection and development of the associated disease. What is proposed is a series of models analogous to PBPK modeling in chemical risk assessment, where the transport and kinetics of the pathogens will be modeled. Using the microbial growth kinetics for each organism a model can be developed describing the multiplication of the organisms. Since these are both primarily respiratory pathogens, the transport of the pathogens through the respiratory tract can be modeled as the pathogens are being transported in the bulk fluid to the site in the respiratory tract which is most susceptible location (alveolar macrophage for *B. anthracis*. Once the pathogen has been transported to the susceptible location each of these must use intracellular transport in order to get to the location where the full infection and disease progression can be initiated (alveolar macrophage for *B. anthracis*. All of these processes can be modeled within an engineering modeling framework and the overall effect on the dose inhaled can be modeled stochastically. These processes will generate an effective dose rather than a static dose that is currently used in microbial risk assessment.

Contribution:

Not only can the dose response be adapted for physical transport but also for microbial kinetics. Also by not requiring an additional parameter into the dose response models defends the linear low dose assumption which is inherent to the currently used dose response models (exponential and beta Poisson)

Results:

The dose has been adapted from an exposed dose to a delivered dose and a pathogen burden as well. Each of these corrections are linear requiring only a simple correction factor without the need of including an additional parameter into the dose response models. This main result also demonstrated that the linear low dose assumption is valid, due to the proof that there was no need for an additional parameter in the dose response models. These results were discovered based on the knowledge that the dose inhaled in a malicious or natural pathogen release is not necessarily the dose that is causing the disease. There exist a number of mechanisms that allow for the dose to be reduced or in some cases with rapid multiplication increase. By examining the pathogenesis of *Bacillus anthracis* (*B. anthracis*) it can be seen that pathogens have defined routes of infection and development of the associated disease. What has been developed is a series of models analogous to PBPK modeling in chemical risk assessment, where the transport and kinetics of the pathogens has been modeled. Using the microbial growth kinetics for each organism a model can be developed describing the multiplication of the organisms. Since this is primarily a respiratory pathogen, the transport of the pathogens through the respiratory tract can be modeled as the pathogens are being transported in the bulk fluid to the site in the respiratory tract which is most susceptible location (alveolar macrophage for *B. anthracis*. Once the pathogen has been transported to the susceptible location intracellular transport must be utilized in order to get to the location where the full

infection and disease progression can be initiated (alveolar macrophage for *B. anthracis*). All of these processes can be modeled within an engineering modeling framework and the overall effect on the dose inhaled can be modeled effectively. These processes have generated an effective dose rather than a static dose that is currently used in microbial risk assessment.

Development of Physiologically Based Dose Response Models - LUs (751, 756):
Things that are in progress - LU (751)
Author(s): Mark Weir
and Things that I have completed - LU (756)
Author(s): Mark Weir
When Modeling Physiology and Kinetics we wanted to find out If all of these processes can be modeled and if there is an affect on the associated dose response models
Experimental Design:
I will determine available data so that a two stage model can be developed which will model the inhalation and transport and kinetics of the pathogenesis of inhaled *Bacillus anthracis* spores.
Contribution:
Not only can the dose response be adapted for physical transport but also for microbial kinetics. Also by not requiring an additional parameter into the dose response models defends the linear low dose assumption which is inherent to the currently used dose response models (exponential and beta Poisson)
Results:
The dose has been adapted from an exposed dose to a delivered dose and a pathogen burden as well. Each of these corrections are linear requiring only a simple correction factor without the need of including an additional parameter into the dose response models. This main result also demonstrated that the linear low dose assumption is valid, due to the proof that there was no need for an additional parameter in the dose response models. These results were discovered based on the knowledge that the dose inhaled in a malicious or natural pathogen release is not necessarily the dose that is causing the disease. There exist a number of mechanisms that allow for the dose to be reduced or in some cases with rapid multiplication increase. By examining the pathogenesis of *Bacillus anthracis* (*B. anthracis*) it can be seen that pathogens have defined routes of infection and development of the associated disease. What has been developed is a series of models analogous to PBPK modeling in chemical risk assessment, where the transport and kinetics of the pathogens has been modeled. Using the microbial growth kinetics for each organism a model can be developed describing the multiplication of the organisms. Since this is primarily a respiratory pathogen, the transport of the pathogens through the respiratory tract can be modeled as the pathogens are being transported in the bulk fluid to the site in the respiratory tract which is most susceptible location (alveolar macrophage for *B. anthracis*. Once the pathogen has been transported to the susceptible location intracellular transport must be utilized in order to get to the location where the full infection and disease progression can be initiated (alveolar macrophage for *B. anthracis*). All of these processes can be modeled within an engineering modeling framework and the overall effect on the dose inhaled can be modeled effectively. These processes have generated an effective dose rather than a static dose that is currently used in microbial risk assessment.

Dose-response model for influenza A virus - LUs (294, 912):
Things that are in progress - LU (294)
Author(s): Toru Watanabe

and Things that I have completed - LU (912)
Author(s): Toru Watanabe
When Modeling dose response model we wanted to find out 1) Dose-response model for influenza A virus. 2) Relationship between taxonomy of influenza A virus and its infectivity (or virulence).

Experimental Design:
1) Collecting datasets for human infection with various strains of influenza A virus. 2) Fitting dose-response models to the datasets. 3) Evaluating infectivity (or virulence) of each virus strain and comparing them focusing on the taxonomy of influenza A virus.

Results:
Dose-response relationships of eleven live attenuated reassortants of influenza A virus could be described by a beta-Poisson model. Pooling analysis revealed that virus subtype (H1N1 or H3N2) and human age (adults or children) were significant factors determining the dose-response relationship, while attenuation method (cold-adapted or avian-human gene reassortment) affected only the relationship of H1N1 virus infection to adults. The datasets for H3N2 wild-type virus could be successfully pooled with those for its reassortants on the assumption that the gene reassortment attenuates wild-type virus by 770 times. Considering this degree of attenuation, 10% infectious dose of H3N2 wild-type virus for adults was estimated at 25 TCID50. The infectivity of wild-type H1N1 virus was still unknown since the dataset pooling was failed.

3. Modeling the effect of multiple doses of scrapie agent - LUs (742, 445):
Things that are in progress - LU (742)
Author(s): Yin Huang
and Things that I have progress - LU (445)
Author(s): Yin Huang
Initially Modeling dose response we wanted to find out Time-dose-response model could provide significantly acceptable fit to the human morbidity dose-response data and its modified form could be fitted with the response data of multiple-dose challenges in order to quantify the effect of different dosing schedules.
The original Experimental Design was as follows:
Time-dose-response model could provide significantly acceptable fit to the human morbidity dose-response data and its modified form could be fitted with the response data of multiple-dose challenges in order to quantify the effect of different dosing schedules. We are currently trying to find out. The modified form of the time-dose-response model could provide statistically acceptable fit to the response data of multiple-dose challenge of scrapie agent.
The current Experimental Design is as follows:
1) Collecting survival dose-response data of multiple challenge 2) Further developing the current time-dose-response models to describe the probability of response caused by different dosing schedules

Modeling the effect of multiple doses of *Francisella tularensis* - LUs (743, 742):
Things that are in progress - LU (743)
Author(s): Yin Huang
and Things that I have progress - LU (742)
Author(s): Yin Huang
Initially Validating dose response we wanted to find out The modified form of the time-dose-response model could provide statistically acceptable fit to the response data of multiple-dose challenge of scrapie agent.
The original Experimental Design was as follows:

The modified form of the time-dose-response model could provide statistically acceptable fit to the response data of multiple-dose challenge of scrapie agent.
We are currently trying to find out. The modified form of the time-dose-response model could provide statistically acceptable fit to the response data of multiple challenge of *Francisella tularensis*.
The current Experimental Design is as follows:
1) MSU will be conducting the experiment on survival dose response of animals repeatedly challenged by *Francisella tularensis* 2) We will analyze the MSU data by using our modified time-dose-response models to describe the probability of response caused by different dosing schedules

4. Equine Encephalitis Data Files - LUs (446, 635):
   Things that are in progress - LU (635)
   Author(s): Sharon Nappier
   and Things that I have completed - LU (446)
   Author(s): Sharon Nappier
   Once we learned:
   Venezeualan, Western, and Equine encephalitis viruses could be pooled by the intracranial route using a modified beta-Poisson dose response model with an age-dependency parameter.
   This result led us to the following research question Collecting data we wanted to find out We are trying to determine the maximum likelihood estimates and best fit to the data.
   The current Experimental Design is as follows:
   fit data with exponential, beta-poisson, and log-probit models.

   R code for Equine Encephalitis Viruses Dose Response Models - LUs (446, 636):
   Things that are in progress - LU (636)
   Author(s): Sharon Nappier
   and Things that I have completed - LU (446)
   Author(s): Sharon Nappier
   Once we learned:
   Venezeualan, Western, and Equine encephalitis viruses could be pooled by the intracranial route using a modified beta-Poisson dose response model with an age-dependency parameter.
   This result led us to the following research question Calculating dose response we wanted to find out. We are trying to determine if the data fit the dose-response models using the attached R code.
   The current Experimental Design is as follows:
   Use the attached R code to determine how the data fit the dose-response models.

8. Outputs:
   1. Students Supported:
      Yin Huang PhD. Candidate, supervisor: Dr. Charles N. Haas
      Sushil Tamrakar PhD. Candidate, supervisor: Dr. Charles N. Haas

   2. Students Graduated:
      Mark H. Weir earned his PhD. in Environmental Engineering
      Mark H. Weir who assisted Project III with dose response modeling graduated with his PhD. in Environmental Engineering in Summer 2009 with the thesis "Development of a Physiologically Based Pathogen Transport and Kinetics Model for Inhalation of *Bacillus*

anthracis spores."

3. Publications:
Incorporating time post inoculation into a dose response model of *Yersinia pestis* in mice
Huang, Y., Bartrand, T.A., Haas, C.N. and Weir M.H. 2009. Incorporating Time Post Inoculation into a Dose-Response Model of *Yersinia pestis* in Mice. Journal of Applied Microbiology. 107(3):727-735.

Time-dose-response Models for Microbial Risk Assessment
Huang, Y. and Haas, C.N. 2009. Time-dose-response Models for Microbial Risk Assessment. Risk Analysis. 29(5): 648-661.

How Sensitive Is Safe? Risk-Based Targets for Ambient Monitoring of Pathogens
Huang, Y., Hong, T., Bartrand, T.A., Gurian, P.L., Haas, C.N., Liu, R., and Tamrakar, S.B. 2009. How Sensitive Is Safe? Risk-Based Targets for Ambient Monitoring of Pathogens. IEEE Sensors Journal. Accepted for publication.

Incorporating age into the current dose response models
Weir M.H., Haas, C.N. (In Press.) Quantifying the Effect of Age on the Dose Response of *Variola major* in Suckling Mice. Human and Ecological Risk Assessment.

4. Patents:
5. Presentations:
A dose-response model for equine encephalitis viruses, with age susceptibility quantification. Poster presentation was given at the DHS student summit in March, 2009 by Sharon Nappier.

Benefit-cost analysis to develop targets for ambient air sampling
Huang Y., T. Hong, P. L. Gurian, C. N. Haas, T. Bartrand, S. Tamakar, and M.H. Weir. Benefit-cost analysis to develop targets for ambient air sampling. Society for Risk Analysis Annual Meeting. Boston, MA. December 7-10, 2008.

Dose-response Time Modeling
Huang, Y and Haas, C.N. Dose-response Time Modeling. The Third Annual Department of Homeland Security University Network Summit on Research and Education. Washington DC. March 17-19, 2009.

Quantification of the Temporal Effect on *Mycobacterium tuberculosis* Infection by Time-dependent Dose-response Models
Huang, Y and Haas, C.N. Quantification of the Temporal Effect on *Mycobacterium tuberculosis* Infection by Time-dependent Dose-response Models. 110th General Meeting of the American Society for Microbiology. Philadelphia, PA. May 17 - 21, 2009.

Development of Physiologically Based Dose Response Models for Inhalational Anthrax;
Mark H. Weir and Charles N. Haas; Society for Risk Analysis Annual Meeting. Baltimore Maryland. December, 2009.

Development of Physiologically Based Dose Response Models for Inhalational Anthrax;
Mark H. Weir and Charles N. Haas; Association of Environmental Engineering and Science Professors; 2009 Conference. Iowa City, IA. July, 2009.

Including Pathogenesis and Transport Physics for Inhalation Dose Response of *Bacillus anthracis*; Mark H. Weir and Charles N. Haas; Department of Homeland Security, Science and Technology Directorate, Office of University Programs; Annual University Network Summit on Research and Education. Washington DC. March, 2009.

Tularemia Dose Response Analysis for Oral Exposure of Multiple Strains; Mark H. Weir and Charles N. Haas; Department of Homeland Security, Science and Technology Directorate, Office of University Programs; Annual University Network Summit on Research and Education. Washington DC. March, 2009.

Microbial Dose Response Modeling for the 21st Century: Development of Mechanistic Dose Response Models; Mark H. Weir and Charles N. Haas; Society of Risk Analysis Annual Meeting. Boston, MA. December, 2008.

6. Organization of workshops:
7. Participation in workshops:
   Charles N. Haas and Mark H. Weir instructed during the 4th QMRA summer institute.

8. Case studies algorithms developed:
9. Algorithms developed:
10. Human Resource Development:
11. Funds Leveraged:
12. Other:
    Data used for the dose-response analysis for *Coxiella burnetii* (Q fever)
    Usable data were mined in open literature and tested test of trend.

9. Outcomes:
   Unit 294: 1) The model will enable us to evaluate the risk of infection with influenza A virus. 2) There is a possibility that risk of human infection with avian influenza virus like H5N1 virus could be evaluated based on taxonomical relationship.

   Unit 311: Q-fever is caused by bacterium "*Coxiella burnetii*" . Many investigators have estimated that less than 10 organisms were enough to infection a person. The potential out come of the study will be: 1) dose- response model and low dose estimation and 2) estimation of number of organism that may infect a person.

   Unit 386: Development of dose response relations for estimation of human risk.

   Unit 437: Dose-response relationship identified for Venezuelan, Western, and Eastern encephalitis viruses.

   Unit 445: Time-dose-response model might describe and predict the data fairly accurately and the outcomes could be used for the improved post-exposure decision making or as a component to better assist epidemiological investigations.

   Unit 446: The best dose-response model fits and LD50s/LD10s were determined. Multiple viruses and multiple routes were pooled with and without modified age-dependent dose-response models.

   Unit 635: The data will likely fit to either the exponential or beta-poisson models. We might also

find age-dependency relationships in the data.

Unit 636: Find best-fits of the data to dose-response models. Identify if dose-response parameters change with mouse age.

Unit 640: From the listed journal articles, we can mine the animal experiment data that can be used for dose-response modeling. Moreover, those articles will provide in depth knowledge of diseases and pathogenesis and pathophysiology of infection in different animals.

Unit 646: the data were used in dose-response analysis.

Unit 649: Using the classical model of dose-response model, dose-response model for *Burkholderia pseudomallei* could be developed so that we will be able to predict the minimum or median infective dose.

Unit 655: The modified dose-response models that can incorporate multi-routes correction factor/s and interspecies correction factor/s. If we have information (data) of one route, we will be able to predict the risk from another route/s. Similarly, we will be extrapolating one species (strain) of pathogens to another and one host to other.

Unit 659: The data of response of hamsters infected by multiple oral challenges with scrapie agent from Diringer's study can be used to validate our model describing the cumulative response caused by challenges at multiple time points.

Unit 662: A understanding and assessment of how the particle size affects the dose response of inhalation anthrax show in accomplishment unit number 287 and things that I have completed learning unit 609.

Unit 741: This can be compared with Diringer's study (unit 659). The difference between these two studies may demonstrate the importance of the influence of exposure route on animal response to scrapie agent.

Unit 742: The suggested model could be able to quantify the effect of different dosing schedules of scrapie agents. The resulting model can be used for describing the repeated infections by other pathogens.

Unit 743: The resulting model could be able to quantify the effect of different dosing schedules on the animals exposed to *Francisella tularensis*, which would contribute to current dose-response analyses. This is important because in reality the multiple exposure is common.

Unit 751: new framework of modeling dose response where physiology and microbial kinetics will be included.

Unit 756: New framework of modeling the bulk fluid transport and microbial kinetics for pathogens in dose response models.

Unit 912: Dose-response model for H3N2 influenza A virus. A method to estimate the degree of attenuation of wild-type virus due to gene reassortment for vaccine development.

10. Integration with other projects:
    An association was created between Unit 609, authored by Mark Weir (Project III, Drexel

University) and Unit 469, authored by Patrick Gurian (Project IV, Drexel University).

An association was created between Unit 484, authored by Rachael Jones (Project I, U of California Berkeley) and Unit 481, authored by Shamia Hoque (Project III, Drexel University).

An association was created between Unit 481, authored by Shamia Hoque (Project III, Drexel University) and Unit 487, authored by Christopher Choi (Project I, U of Arizona).

An association was created between Unit 609, authored by Mark Weir (Project III, Drexel University) and Unit 530, authored by Patrick Gurian (Project IV, Drexel University).

An association was created between Unit 521, authored by Mark Weir (Project III, Drexel University) and Unit 540, authored by Jade Mitchell-Blackwood (Project IV, Drexel University).

An association was created between Unit 609, authored by Mark Weir (Project III, Drexel University) and Unit 540, authored by Jade Mitchell-Blackwood (Project IV, Drexel University).

An association was created between Unit 352, authored by Scott McLennan (Project V, Michigan State U) and Unit 669, authored by Mark Weir (Project III, Drexel University).

11. Anticipated Technical Results and Developments:

CAMRA Report for Year IV (September 15, 2008 to September 14, 2009) for Project IV

1. Project IV
2. Investigators: Patrick Gurian, Mark H. Weir, Elizabeth Casman, Jade Mitchell-Blackwood, Scott McLennan , Tao Hong, Nicholas Ward, David Durham
3. Project Goals:
   Use a scenario-based approach to identify key decision points and uncertainties in bioterrorism risk management plans.
   Develop statistical descriptions of uncertainty in model parameters.
   Identify strategies to reduce uncertainty and manage bioterrorism risk.
4. Tasks for Year IV (September 15, 2008 to September 14, 2009):

Dr Elizabeth Casman's Laboratory (Carnegie Mellon)

Recruitment of 20 subjects.
Semi-structured interviews.
Transcription of interviews.
Coding of interviews.
Create customized coding database.
Train coders to apply expert model to interviews.
Assess reliability of coders during training, goal of 0.8.
Assessment of interview content for conceptual errors.
Complete coding of all interviews plus reliability coding of random set.
Analysis of transcripts.
1. Descriptive statistics with ranges of responses on quantitative questions
2. Convert qualitatively coded data to variables representing concepts from expert model
3. Compare groups of participants in concepts mentioned

4. Compare misconceptions across concepts and groups
5. Identify key points for follow-up assessment with survey
6. Characterize understanding of flu, including limitations and gaps in knowledge
Preliminary analysis and internal CAMRA reports.
Development of survey instrument.
Testing and refinement of survey instrument.
Recruitment of 200 subjects.
Web survey.
Analysis of survey results.

Dr. Patrick L. Gurian's Laboratory (Drexel)

Interpreting environmental sampling for *B. anthracis.*

An integrated model of *B. anthracis* dispersion in an indoor environment and dose-response has been developed to link environmental concentrations with estimates of risk following a release. A paper describing how this approach may be used to set risk-informed environmental standards is now under review. An additional paper describing sampling requirements to meet risk-informed standards is also under review. Further work in this area is described below.

> o Verification Against Release Scenarios: A request for data from testing conducted by U.S. EPA and national labs will be undertaken as well as a literature search. The model has already been verified against the work of Sextro et al. It will be further verified against any additional data obtained.
> o Response to Reviewer Comments: The development of an integrated model requires assumption and may be contentious. Extensive work responding to reviewer comments and/or resubmitting at different journals are anticipated.
> o Identifying sampling strategies which allow characterization of a release. The particulate size distribution of a release is critical to modeling the dispersion and human health risk associated with the release. This work will identify environmental samples needed to identify the particulate size distribution of a release.

- Hierarchical Modeling of Dose Response Variability
Bayesian hierarchical models offer a potential method of accounting for variability in host organism susceptibility, and agent infectivity. An effort to assess interspecies variability among hosts estimated that an interspecies extrapolation uncertainty factor of roughly 10 was appropriate for *B. anthracis* dose response. This uncertainty factor has been used in the risk-informed standard setting effort described in 1 above. Further work in this area is described below.

> o A dataset describing variability in dose response behavior of environmental inoculates will be analyzed to identify suitably health protective estimates of infectivity for risk management decision making.
> o The existing work, which has been presented at the Society for Risk Analysis will be submitted for publication.

- Decision Thresholds for Microbial Risk
Under some scenarios, a release of *B. anthracis* could produce a small, highly impacted area and a large surrounding area with minimal risk. How large an area is subject to remediation and how many people are subject to medical treatment are questions that have substantial health and economic

impacts. This research assesses at what level of risk responses such as remediation and medical treatment become justified based on conventional cost-effectiveness benchmarks for risk reduction. The literature review and model development are now complete. Preliminary results were presented at the Society for Risk Analysis Annual Meeting in December 2008.

> o Work in this year will focus on documenting the results in a manuscript and submitting the manuscript for publication.

To the extent that resources allow, decision models will be constructed for norovirus, influenza, and Cryptosporidium that integrate knowledge from across the CAMRA center. Completing these in Year 4 depends on the availability of leveraged resources from students in graduate classes and CAMRA's summer institute. If successfully completed in Year 4, this would represent early completion of the cross-project risk assessments for the CAMRA center. If not completed, core project resources will be used to complete at least two of these in Year 5. In combination with the existing work on anthrax and plague, this will achieve the goal of completing a total of four cross-project risk assessments over the five year center duration.

5. Research Activities:

Researcher Name	Research Activity
Patrick L. Gurian	Creating modeling method
	Modeling transmission
	Evaluating decisions
	Creating analysis tool
	Analyzing decisions
	Estimating dose response model
Elizabeth Casman	Conducting mental models study
	Constructing mental models
Jade Mitchell Blackwood	Modeling dose response
S. Devin McLennan	Analyzing data
	Modeling transmission
	Calculating risk threshold
Tao Hon g	Modeling fate and transport
	Identifying fate and transport

6. Background and prior research:
   Previous research had been focused on model development, principally 1) a Bayesian hierarchical dose response model and 2) a coupled indoor air particulate transport model and microbial inhalation risk model. These previous efforts provided the computational engines for the results generated during the current reporting period.

7. Research Contributions this Year:
   1. Integrated Transport and Risk Model Things that are in progress - LU (422):
      Author(s): Tao Hong
      When Modeling fate and transport we wanted to find out The distribution of *Bacillus anthracis* in an office suite after releasing
      Experimental Design:
      Model is built based on a simple office suite with a heating ventilation and air conditioning (HVAC) system. We divide the office into 7 internal compartments: air, tracked floor, untracked floor, walls, ceiling, HVAC, and the nasal passages of an occupant of the office. In order to obtain mass-balance closure, we add another compartment to the system consisting of all areas external to the room. We obtain the following system of linear first order ordinary differential equations based on using the mass balance relationships among different compartments in the office suite. We obtain the following system of linear first order ordinary differential equations based on using the mass balance relationships among different compartments in the office suite.

      Persistence Model Estimation and Selection Things that are in progress - LU (458):
      Author(s): Patrick Gurian
      When Creating modeling method we wanted to find out Determine which decay models best describe data which CAMRA has generated.
      Experimental Design:
      An Excel spreadsheet will be developed to fit candidate models of persistence on fomites.

      Cost-effectiveness of Influenza Control Things that are in progress - LU (771):
      Author(s): Patrick Gurian, Joe Eisenberg, Ian Spicknall
      When Modeling transmission we wanted to find out Which non-pharmaceutical interventions are appropriate for controlling influenza transmission in schools?
      Experimental Design:
      A group at the Summer Institute conducted a case study of different methods of controlling influenza transmission looking at cost-effectiveness of different strategies.

      Identifying sampling strategies Things that are in progress - LU (776):
      Author(s): Tao Hong
      When Identifying fate and transport we wanted to find out Model identifiability analysis is used to assess the appropriate degree of model complexity and provide guidance for environmental sampling of well-mixed interior areas of buildings.

      Valuing Environmental Detection of Bacillus anthracis Things that are in progress - LU (806):
      Author(s): Patrick Gurian
      When Evaluating decisions we wanted to find out When should environmental monitoring be conducted?
      Experimental Design:
      The costs of a *Bacillus anthracis* release will be evaluated with and without an

environmental detection system.

Cryptosporidium boil water threshold risk Things that are in progress - LU (813):
Author(s): Patrick Gurian
When Analyzing decisions we wanted to find out The action level of risk for issuing a boil water order.
Experimental Design:
A benefit-cost analysis will be conducted of the decision to issue a boil water order in response to potential exposure to cryptosporidium.

2. Integrated Transport and Risk Model - LUs (422, 423):
Things that are in progress - LU (422)
Author(s): Tao Hong
and Things that I have completed - LU (423)
Author(s): Tao Hong
When Modeling fate and transport we wanted to find out The distribution of *Bacillus anthracis* in an office suite after releasing
Experimental Design:
Model is built based on a simple office suite with a heating ventilation and air conditioning (HVAC) system. We divide the office into 7 internal compartments: air, tracked floor, untracked floor, walls, ceiling, HVAC, and the nasal passages of an occupant of the office. In order to obtain mass-balance closure, we add another compartment to the system consisting of all areas external to the room. We obtain the following system of linear first order ordinary differential equations based on using the mass balance relationships among different compartments in the office suite. We obtain the following system of linear first order ordinary differential equations based on using the mass balance relationships among different compartments in the office suite.

Plague equilibria in urban rat populations - LUs (426, 428):
Things that are in progress - LU (426)
Author(s): Scott McLennan , Elizabeth Casman
and Things that I have completed - LU (428)
Author(s): Scott McLennan , Elizabeth Casman
When Modeling transmission we wanted to find out The conditions necessary for plague to persist in an urban rate population.
Experimental Design:
Key ecological factors in the transmission and persistence of plague in urban rate populations will be modeled with differential equations. Equilibrium states will be explored, and variables controlling equilibria identified.
Contribution:
We derived a mathematical expression characterizing the tendency for bubonic plague to become established in an urban rat population upon introduction. The expression gives a threshold condition for plague persistence in terms of measurable attributes of a local urban rat population: the average flea density and the rat colony size. If the local rat population exceeds this threshold, plague circulation is predicted to continue; if not, it will burn out of its own accord. This expression may be used to evaluate both the vulnerability of a specific neighborhood and the effect of pest control strategies upon that vulnerability, issues of increasing relevance considering the recent proliferation of laboratories involved in select agent research.
Results:
Developed quantitative expression for estimating plague transmission stability in urban

rat populations.

Cost-effectiveness of Influenza Control - LUs (771, 772):
Things that are in progress - LU (771)
Author(s): Patrick Gurian, Joe Eisenberg, Ian Spicknall
and Things that I have completed - LU (772)
Author(s): Patrick Gurian
When Modeling transmission we wanted to find out Which non-pharmaceutical interventions are appropriate for controlling influenza transmission in schools?
Experimental Design:
A group at the Summer Institute conducted a case study of different methods of controlling influenza transmission looking at cost-effectiveness of different strategies.
Contribution:
In this context hand washing was not effective but masks and surface cleaning were.
Results:
A draft report was developed by students at the summer institute

Identifying sampling strategies - LUs (776, 778):
Things that are in progress - LU (776)
Author(s): Tao Hong
and Things that I have completed - LU (778)
Author(s): Tao Hong
When Identifying fate and transport we wanted to find out Model identifiability analysis is used to assess the appropriate degree of model complexity and provide guidance for environmental sampling of well-mixed interior areas of buildings.
Results:
The results indicate that if samples are taken in a single well-mixed room then neither a 4-particle-size model nor a 3-particle-size model can be identified by aggregate sampling of available environmental compartments. If sampling is extended to a second room, which has been contaminated by air flow through the HVAC system, then it is still not possible to identify a 4-particle-size model. However, it is possible to identify a 3-particle-size model. The three particle sizes proposed for modeling are 1 Î¼m particulates, which would account for much of the risk outside the building due to their potential for long range transport, 3-5 μm particles which are respirable but are removed more readily by deposition and HVAC filters than smaller particles, and 10 Î¼m particles which are not readily respirable and settle relatively quickly. Modeling these three categories is proposed as a means to distinguish between the hazards posed by different sizes of aerosols while reducing model complexity to a point where necessary inputs can be identified by aggregate sampling methods.

Valuing Environmental Detection of *Bacillus anthracis* - LUs (806, 807):
Things that are in progress - LU (806)
Author(s): Patrick Gurian
and Things that I have completed - LU (807)
Author(s): Patrick Gurian
When Evaluating decisions we wanted to find out When should environmental monitoring be conducted?
Experimental Design :
The costs of a Bacillus anthracis release will be evaluated with and without an environmental detection system.
Contribution:

Monetized estimates of the value of early detection are provided.
Results:
Guidelines are provided for valuing environmental detection as a function of probability of release and size of event.

Persistence Model Estimation and Selection - LUs (458, 809):
Things that are in progress - LU (458)
Author(s): Patrick Gurian
and Things that I have completed - LU (809)
Author(s): Patrick Gurian
When Creating modeling method we wanted to find out Determine which decay models best describe data which CAMRA has generated.
Experimental Design:
An Excel spreadsheet will be developed to fit candidate models of persistence on fomites.
Contribution:
Inactivation consists of a rapid first phase of 48-72 hours followed by a slower phase.
Results:
We have created a tool to estimate models for microbial inactivation. Models are ranked using a common statistical metric, BIC.

Designing and conducting mental models study - LUs (532, 848):
Things that are in progress - LU (532)
Author(s): Elizabeth Casman
and Things that I have completed - LU (848)
Author(s): Elizabeth Casman
When conducting mental models study we wanted to find out 1) To identify the missing information that people would need to make good decisions regarding risk reduction from bioterrorism attacks. 2) How do expert and lay understanding of self-protective behavioral choices relevant to bioterrorism differ? 3) What information supplied to the lay public would enable them to come to the same conclusions as domain experts? What interview questions will deliver the desired information?
Experimental Design:
a. Coding of interviews 1. Create customized coding database 2. Train coders to apply expert model to interviews 3. Assess reliability of coders during training, goal of 0.8 4. Assessment of interview content for conceptual errors 5. Complete coding of all interviews plus reliability coding of random set b. Analysis of transcripts 1. Descriptive statistics with ranges of responses on quantitative questions 2. Convert qualitatively coded data to variables representing concepts from expert model 3. Compare groups of participants in concepts mentioned
Contribution:
Identified key concepts related to behaviors concerning the interruption of flu transmission.
Results:
Processed interview tapes: transcription, coding to expert model, reliability check of coding, entry into excel, flagged erroneous concepts. Began data analysis: statistical and graphical analysis of information in interviews. Collected and organized flu transmission risk literature into influence diagram which will help identify lay people's information needs.

Hierarchical Modeling of Dose Response Variability - LUs (840, 853):
Things that are in progress - LU (840)

Author(s): Jade Mitchell-Blackwood
and Things that I have completed - LU (853)
Author(s): Jade Mitchell-Blackwood
When Modeling dose response we wanted to find out It is hypothesized that using the Bayesian hierarchical framework a set of health protective estimates of infectivity for risk management decision making can be generated.
Experimental Design:
A dataset describing variability in dose response behavior of environmental inoculates will be analyzed to identify suitably health protective estimates of infectivity for risk management decision making.
Contribution:
This unit completes the tasks in unit 840.
Results:
This unit completes the tasks in unit 840.

3. Designing and conducting mental models study - LUs (532, 537):
    Things that are in progress - LU (532)
    Author(s): Elizabeth Casman
    and Things that I have progress - LU (537)
    Author(s): Elizabeth Casman
    Initially conducting mental models study we wanted to find out To produce a diagram representing all plausible flu transmission pathways and the methods people and institutions employ to interrupt flu transmission.
    The original Experimental Design was as follows:
    To produce a diagram representing all plausible flu transmission pathways and the methods people and institutions employ to interrupt flu transmission.
    We are currently trying to find out 1) To identify the missing information that people would need to make good decisions regarding risk reduction from bioterrorism attacks. 2) How do expert and lay understanding of self-protective behavioral choices relevant to bioterrorism differ? 3) What information supplied to the lay public would enable them to come to the same conclusions as domain experts? What interview questions will deliver the desired information?
    The current Experimental Design is as follows:
    a. Coding of interviews 1. Create customized coding database 2. Train coders to apply expert model to interviews 3. Assess reliability of coders during training, goal of 0.8 4. Assessment of interview content for conceptual errors 5. Complete coding of all interviews plus reliability coding of random set b. Analysis of transcripts 1. Descriptive statistics with ranges of responses on quantitative questions 2. Convert qualitatively coded data to variables representing concepts from expert model 3. Compare groups of participants in concepts mentioned

    Hierarchical Modeling of Dose Response Variability – Lus (840, 540):
    Things that are in progress - LU (840)
    Author(s): Jade Mitchell-Blackwood
    and Things that I have completed – LU (540)
    Author(s): Jade Mitchell-Blackwood
    Initially Modeling dose response we wanted to find out It was hypothesized that given the consistency of parameter estimates across different species found by Project 3, the Bayesian hierarchical model predictions will not be overly sensitive to the specification of the prior distribution.
    Experimental Design:

It was hypothesized that given the consistency of parameter estimates across different species found by Project 3, the Bayesian hierarchical model predictions will not be overly sensitive to the specification of the prior distribution.

We are currently trying to find out It is hypothesized that using the Bayesian hierarchical framework a set of health protective estimates of infectivity for risk management decision making can be generated.

Current Experimental Design:

A dataset describing variability in dose response behavior of environmental inoculates will be analyzed to identify suitably health protective estimates of infectivity for risk management decision making.

4. Analyzing Interview Responses for Mental Models Study - LUs (207, 424):
   Things that are in progress - LU (424)
   Author(s): Scott McLennan , Elizabeth Casman
   and Things that I have completed - LU (207)
   Author(s): Elizabeth Casman
   Once we learned:
   These tasks produced a database that allows us to analyze the interview responses
   This result led us to the following research question Analyzing data we wanted to find out If the general public, and members of high-risk occupations in particular, have correct information or important misconceptions about the spread and prevention of influenza.
   Experimental Design:
   The factors in the expert model were given numerical codes. This coding system was used to code the interviews. When a concept or factor is mentioned by an interviewee, it is given the corresponding code from the expert model. The code is scored for correctness (compatibility with expert understanding). The resulting numerical data base will be used for analyzing the lay publicï¿½??s understanding of the scenario and the choices they would face, in particular, where gaps in understanding or misconceptions would have negative consequences.

   Plague equilibria in urban rat populations - LUs (372, 426):
   Things that are in progress - LU (426)
   Author(s): Scott McLennan , Elizabeth Casman
   and Things that I have completed - LU (372)
   Author(s): Sheng Li
   Once we learned:
   These insights provide a theoretical context to examine the role of the environment in pathogen transmission; and our modeling framework provides a means to interpret environmental data to inform environmental interventions.
   This result led us to the following research question Modeling transmission we wanted to find out The conditions necessary for plague to persist in an urban rate population.
   Current Experimental Design:
   Key ecological factors in the transmission and persistence of plague in urban rate populations will be modeled with differential equations. Equilibrium states will be explored, and variables controlling equilibria identified.

8. Outputs:
   1. Students Supported:
      Students Supported and/or Graduated:

Primary support from CAMRA:
Tao Hong, M.S. 2009, Ph.D. in progress
Ryan Wittke (summer 2009), B.S. 2009
Sidra Ahmet (summer 2009), B.S. in progress

Students contributing to CAMRA but with primary support from outside CAMRA

Cara O'Donnell, MPH 2009
April Wright, MPH 2009
John Madsen, MPH 2009
Jade Mitchell-Blackwood, Ph.D. in progress

2. Students Graduated:
   June 2009 MPH graduates
   Cara O`Donnell, April Wright, and John Madsen received their MPHs and completed her microbial risk assessment specialization coursework in June 2009. All participated in CAMRA research activities over the course of their studies.

   Spring 2009 M.S. graduate
   Tao Hong
   A Master thesis was finished entitled "Estimating risk of exposure to *Bacillus anthracis* based on environmental concentrations" which could be found via the following link: http://hdl.handle.net/1860/3012

3. Publications:

   Paper on Neighborhood Water Treatment Systems
   Corella-Barud, V., K.D. Mena, S.G. Gibbs, P.L. Gurian, and A. Barud. 2009. Evaluation of Neighborhood Treatment Systems for Potable Water Supply. International Journal of Environmental Health Research. 19(1):49-58.

   Paper Risk Analysis
   D.P. Durham and E. A. Casman. (In Press.) Threshold Conditions for Bubonic Plague Persistence in Urban Rats. Risk Analysis.

   White Paper Submitted in Support of the Physiologic Assessment of Microbial Effects (PhAME) Project
   A White-Paper was submitted to USACCHPM and is currently pending security clearance for public release of the information. Jade Mitchell-Blackwood and Patrick L. Gurian. Development of Dose-Response Curves for *Bacillus anthracis* (Inhalation Anthrax) Using a Bayesian Approach on Historic Data.

   White Paper Submitted in Support of the Physiologic Assessment of Microbial Effects (PhAME) Project, Limited Distribution through the U.S. Army Center for Health Promotion and Preventive Medicine, Environmental Health Risk Assessment Program (MCHB-TS-REH). Aberdeen Proving Ground, MD. 2008.

   Key uncertainties in risk informed standards for *B. anthracis*
   After a series of bioterrorism-related anthrax attacks in 2001, how to accurately estimate the risk of mortality after exposure to *B. anthracis* is a major concern. Since in many cases human health risk from biological agents is associated with aerosol exposures,

concentrations found on surfaces may be used to infer future or past aerosol exposures. In this paper, we assume that *B. anthracis* spores were released in a one compartment office suite which was connected by HVAC system. A sensitivity analysis is conducted to indentify the key parameters and uncertainties in assessing surface concentration corresponding to certain risk. This provides a background analysis for prioritizing research aimed at reducing these uncertainties.

Huang, Y., Hong, T., Bartrand, T.A., Gurian, P.L., Haas, C.N., Liu, R., and Tamrakar, S.B. 2009. How Sensitive Is Safe? Risk-Based Targets for Ambient Monitoring of Pathogens. IEEE Sensors Journal. Accepted for publication.

4. Patents:
5. Presentations:

Presentation on recovery of spores from filters
April Wright, Patrick L. Gurian, Hernando Perez, and David Greenberg. Bacterial Recovery from HVAC System Filters, American Society for Microbiology. Philadelphia, PA. May 2009.

Presentation on Risk Communication
E. Casman, "Risk Communication Planning for the Aftermath of a Plague Bioattack." Joint U.S. Environmental Protection Agency and Department of Homeland Security Conference on Real-World Applications and Solutions for Microbial Risk Assessment. Bethesda, MD. April 8-10, 2008.

Mitchell-Blackwood, J. "Benefit-cost assessment of the level of risk at which prophylactic antibiotic treatment of anthrax passes a benefit-cost test." Oral presentation at the Society of Risk Analysis Annual Meeting. Boston, MA. December, 2008. - Winner of the Biological Stressors Student Merit Award

Mitchell-Blackwood, J. "Finding Risk Based Switchover Points for Response Decisions for Environmental Concentrations of *Bacillus anthracis*" Presentation at the Drexel Engineering Research Symposium. March 20, 2009.

Mitchell-Blackwood, J. "Finding Risk-Based Switchover Points for Response Decisions for Environmental Exposure to *Bacillus anthracis*" Presentation at The Third Annual DHS University Network Summit. March 17-19, 2009.

Mitchell-Blackwood, J. "Decision Science and Microbial Risk: Intervention Decision Modeling for Airborne *Bacillus anthracis* Release: Which Response and When?" Presentation of results at CAMRA All PI Meeting at EPA. October 22, 2009.

Mitchell-Blackwod, J. "Using An Economic Model to Inform Response Decisions for Environmental Concentrations of *B. anthracis*" Poster presented Association of Environmental Engineering and Science Professors Conference. Iowa City, IA. July, 2009.

6. Organization of workshops:
7. Participation in workshops:
Patrick L. Gurian participated as an instructor at the 4th QMRA summer institute

8. Case studies algorithms developed:
   Summer Institute Case Study of Influenza Control Measures
   The student team used a Project II influenza environmental transmission model to estimate the effectiveness of alternative non-pharmaceutical infection control strategies. Hand washing was found to be ineffective given the scenario and modeling assumptions made. Both environmental surface cleaning and mask use showed benefits that are justified by conventional cost-effectiveness benchmarks.
   Accomplishments by Patrick Gurian.

9. Algorithms developed:
   Persistence model selection spreadsheet.
   A software tool has been developed for the analysis of microbial inactivation data.

10. Human Resource Development:
11. Funds Leveraged:
    CDG support leveraged.
    Funds from a Dept. of Homeland Security Career Development Program in Microbial Risk Assessment for Public Security, Safety, and Health were used to support 3 students who assisted in CAMRA Project IV`s research on actionable levels of microbial risk: Cara O`Donnel, April Wright, and John Madsen.
    Accomplishments by Patrick Gurian.

9. Outcomes:
   Unit 424: Public misconceptions corrected through public information campaigns. Qualitative information about compliance with preventative measures may aid disease transmission modeling, cost-benefit analysis, and risk communication tactics.

   Unit 426: The ability to identify rat populations capable of maintaining a plague outbreak, identifying cities at risk from zoonotic plague, devising risk management actions based on plague ecology in urban rats.

   Unit 428: An equation for evaluating the chance of plague persistence in rat populations, an example for deriving equilibrium equations for other zoonotic diseases.

   Unit 458: A tool that microbiologists can use to summarize their data and report estimates for risk modelers.

   Unit 532: The results of this task will identify critical information needs for risk communication.

   Unit 771: Improved understanding of which interventions are appropriate for managing influenza transmission in schools.

   Unit 772: Possible guidance on what control measures are appropriate may be developed when uncertainties in model inputs have been more thoroughly explored.

   Unit 806: This analysis may provide valuations of early warning for different sizes of events and probability of attack.

   Unit 807: This may provide a framework for efforts to provide decision support to those deciding whether to deploy early detection systems for biological agents.

Unit 809: A tool is available for microbiologists to analyze data on persistence of microbes.

Unit 813: guidance for when action should be taken to reduce microbial risk.

Unit 814: Better understanding of dose response can inform standards development and sampling plan design.

Unit 848: Tool for coding interviews

10. Integration with other projects :

An association was created between Unit 207, authored by Elizabeth Casman (Project IV, Carnegie Mellon) and Unit 424, authored by Scott McLennan (Project IV, Michigan State U).

An association was created between Unit 372, authored by Sheng Li (Project II, U of Michigan) and Unit 426, authored by Scott McLennan (Project IV, Michigan State U).

An association was created between Unit 609, authored by Mark Weir (Project III, Drexel University) and Unit 469, authored by Patrick Gurian (Project IV, Drexel University).

An association was created between Unit 469, authored by Patrick Gurian (Project IV, Drexel University) and Unit 478, authored by Mark Nicas (Project I, U of California Berkeley).

An association was created between Unit 609, authored by Mark Weir (Project III, Drexel University) and Unit 530, authored by Patrick Gurian (Project IV, Drexel University).

An association was created between Unit 609, authored by Mark Weir (Project III, Drexel University) and Unit 540, authored by Jade Mitchell-Blackwood (Project IV, Drexel University).

An association was created between Unit 521, authored by Mark Weir (Project III, Drexel University) and Unit 540, authored by Jade Mitchell-Blackwood (Project IV, Drexel University).

An association was created between Unit 748, authored by Ian Spicknall (Project II, U of Michigan) and Unit 762, authored by Patrick Gurian (Project IV, Drexel University).

11. Anticipated Technical Results and Developments:

CAMRA Report for Year IV (September 15, 2008 to September 14, 2009) for Project V

1. Project V
2. Investigators: Testuser9 first name Testuser9 last name, Rosina Weber, Test Ser, Yuan An, Zunyan Xiong, Mark H. Weir, S. Devin McLennan, XuNing Tang, Sidath Gunawardena, Marcia Morelli, Jay Johnson, Thomas Burke, Stephen Morse, Rebecca Parkin, Suresh Pillai, Desiree Linson
3. Project Goals:
Build a web-based knowledge repository to support sharing and leveraging for the CAMRA research community.
Build a web-based data warehouse to make CAMRA data sets available to outside users and to serve as a central repository for QMRA data.

4. Tasks for Year IV (September 15, 2008 to September 14, 2009):

Dr. Weber's Laboratory (Drexel):

Requirements gathering for Data warehouse.
Complete implementation of Version 2.0.
Merge all learning units from version 1.0 to Version 2.0.
Conduct analysis of survey for Version 1.0 and Version 2.0.
Launch Version 2.0 Beta and conduct Usability test.
Revise and launch Stable Version 2.0.
Apply survey and conduct analysis after Version 2.

5. Research Activities

Researchers Name	Research Activity
Rosina Weber	Designing CAMRA Knowledge Repository (KR)
	Testing CAMRA KR
	Implementing CAMRA KR
	Conducting survey
	Implementing systems
	Designing systems
Sidath Gunawardena	Recommending collaborators
Scott McLennan	Collecting data
XuNing Tang	Reviewing models

6. Background and prior research:

Things I have read - LU (698)
Marshall, Prusak and Shpilberg (1996) list these responsibilities that need to be enforced by organizations to prevent failure in KM systems: determine knowledge, enable knowledge collection, represent knowledge, embed knowledge in targeted processes, verify and validate knowledge, oversee knowledge reuse, monitor knowledge transfer, and create infrastructure for the preceding responsibilities.
Marshall, C., Prusak, L. and Shpilberg, D. 1996. Financial Risk and the Need for Superior Knowledge Management. California Management Review. 38(3): 77-101.

Things I have read - LU (410)
This paper demonstrate that: by using genetic algorithm to train a query set, we can retrieve documents more relevant to a given context. Further, these documents will have larger novelty

because of the mutation pool.

Cecchini, R. L., Lorenzetti, C.M., Maguitman, A.G., and Brignole, N.B. 2008. Using genetic algorithms to evolve a population of topic queries. Information Processing and Management. 44: 1863-1878.

7. Research Contributions this Year:

    1. Designing CAMRA Storehouse Things that are in progress - LU (936):
       Author(s): Rosina Weber
       When Designing systems we wanted to find out How to best make available MRA knowledge, information and data produced by CAMRA members throughout the 5 years of CAMRA.
       Experimental Design was as follows:
       (1) Define audience (2) Several requirement gathering meetings (3) Design the system (4) Test the system (5) Launch

       Discovering Patterns of Collaboration for Recommendation Things that are in progress - LU (938):
       Author(s): Sidath Gunawardena
       When Recommending Collaborators we wanted to find out Can existing collections of data on collaborations be used to recommend interdisciplinary collaborations
       Experimental Design was as follows:
       Gather information on past collaborations in the form of interdisciplinary grants Use Apriori algorithm to discover patterns of collaboration Evaluate resulting patterns on their accuracy to recommend collaboration partners

    2. CAMRA Fomite Matrix - LUs (156, 683):
       Things that are in progress - LU (156)
       Author(s): Scott McLennan
       and Things that I have completed - LU (683)
       Author(s): Scott McLennan , David David Greenburg , Charles Gerba, Amanda Herzog, Ryan Sinclair, Jessica Henley
       When Collecting data we wanted to find out Completing this matrix of fomite data illustrates the differences and similarities between fomite studies.
       Experimental Design was as follows:
       Fomite data sets generated by CAMRA investigators were gathered and combined into a single spreadsheet listing all experimental conditions.
       Contribution:
       Earlier compilations had been made for the purpose of specific statistical tests -- this one is complete, reduces assumptions to the minimum, and should be readable and usable by all CAMRA researchers.
       Results:
       The combined data sets from AZ, NAU, and MSU fomite experiments are compiled in a standard format with annotations describing the comparability of variables.

       Designing CAMRA KR version 2.0 (progress) - LUs (559,929):
       Things that are in progress - LU (559)
       Author(s): Rosina Weber
       and Things that I have completed - LU (929)
       Author(s): Rosina Weber
       When Designing CAMRA KR we wanted to find out The final design for the CAMRA

knowledge repository within CAMRA project period until 2010.
Experimental Design was as follows:
Design version 2.0 of the knowledge repository based on - feedback from CAMRA members of their experiences - feedback from funding agencies - recommendations from HCI experts; The design will be composed of sub-tasks: - design learning units interface and submission - design LU review process - design accomplishment units - design search and browsing - design reporting - design visualizations
Contribution:
We learned how to design Version 2.0.
Results:
The design was completed and submitted to implementation.

design and implementation of version 2.0 - LUs (570, 932):
Things that are in progress - LU (570)
Author(s): Rosina Weber
and Things that I have completed - LU (932)
Author(s): Rosina Weber
When Implementing systems we wanted to find out
Experimental Design was as follows:
1. Complete design of Search 2. Complete design of Reporting 3. Complete design of Visualization 4. Merge all learning units from version 1.0 to Version 2.0
Contribution:
Designing such a system with so many functions took twice the time we expected (2 years) plus one year of different problems that postponed the start of design and implementation.
Results:
The design and implementation are complete. Visualization module had to be removed because it failed.

Discovering Patterns of Collaboration for Recommendation - LUs (938, 942):
Things that are in progress - LU (938)
Author(s): Sidath Gunawardena
and Things that I have completed - LU (942)
Author(s): Sidath Gunawardena
When Recommending Collaborators we wanted to find out Can existing collections of data on collaborations be used to recommend interdisciplinary collaborations
Experimental Design was as follows:
Gather information on past collaborations in the form of interdisciplinary grants Use Apriori algorithm to discover patterns of collaboration Evaluate resulting patterns on their accuracy to recommend collaboration partners
Contribution:
Data on past collaborations shows potential as a source of recommending collaboration partners.
Results:
Data on past interdisciplinary collaborations, obtained from NSF and NIH grants, when used to recommend collaboration partners solely based on a subject's research interests had accuracy rates of between 44% and 90%

3. CAMRA KR Version 2.0: Testing - LUs (931, 226):
    Things that are in progress - LU (931)
    Author(s): Rosina Weber

and Things that I have progress - LU (226)
Author(s): Rosina Weber
Initially Testing CAMRA KR we wanted to find out whether there are any bugs or deficiencies in CAMRA Version 2/0
The original Experimental Design was as follows:
whether there are any bugs or deficiencies in CAMRA Version 2/0
We are currently trying to find out whether there are any bugs or deficiencies in CAMRA Version 2/0
The current Experimental Design is as follows:
Perform unit tests of standalone modules of CAMRA KR Version 2.0 is undergoing at the end of Year IV

Survey of CAMRA KR users - pre version 2 - LUs (934, 565):
Things that are in progress - LU (934)
Author(s): Rosina Weber
and Things that I have progress - LU (565)
Author(s): Rosina Weber
Initially conducting survey we wanted to find out This is to be filled in the following unit of the type \'Things that are in progress\', as part of work in this task in year 3.
The original Experimental Design was as follows:
This is to be filled in the following unit of the type \'Things that are in progress\', as part of work in this task in year 3.
We are currently trying to find out A thorough analysis is being conducted as par of the drafting of a manuscript by the experts in Human Computer Interaction.
The current Experimental Design is as follows:
The anonymous survey was submitted to users in Year III all PI meeting.

Launch version 2.0 of CAMRA KR - LUs (935, 568):
Things that are in progress - LU (935)
Author(s): Rosina Weber
and Things that I have progress - LU (568)
Author(s): Rosina Weber
Initially Implementing systems we wanted to find out
The current Experimental Design is as follows:
After testing the system, we will contact all users notifying them of the official launch of Version 2.1 and explain the novelties

8. Outputs:
    1. Students Supported:
    Sidath Gunawardena
    Zunyan Xiong,
    Jay Johnson,
    Xuning Tang
    2. Students Graduated:
    3. Publications:
    Paper on FLAIRS 2009
    Gunawardena, S., and Weber, R. 2009. Discovering Patterns of Collaboration for Recommendation. In Proceedings 22th International FLAIRS Conference, FLAIRS`09. AAAI Press, Menlo Park, CA. 2009.

    Discovering Patterns of Collaboration for Recommendation

Paper presented at FLAIRS conference 2009 Gunawardena, S., and Weber, R. 2009. Discovering Patterns of Collaboration for Recommendation. In Proceedings 22th International FLAIRS Conference, FLAIRS`09. AAAI Press, Menlo Park, CA. 2009.

4. Patents:
5. Presentations:
6. Organization of workshops:
7. Participation in workshops:
8. Case studies algorithms developed:
9. Algorithms developed:
10. Human Resource Development:
11. Funds Leveraged:

9. Outcomes:
   Unit 683: Easy access to compiled fomite data.

   Unit 929: Design of knowledge repository available for use.

   Unit 931: A tested Knowledge repository.

   Unit 932: An implemented knowledge repository.

   Unit 936: One web-source containing all produced by CAMRA.

10. Integration with other projects:
    An association was created between Unit 352, authored by Scott McLennan (Project V, Michigan State U) and Unit 669, authored by Mark Weir (Project III, Drexel University).

    An association was created between Unit 58, authored by Rosina Weber (Project V, Drexel University) and Unit 877, authored by Christopher Choi (Project I, U of Arizona).

11. Anticipated Technical Results and Developments:

Appendix C: Fourth CAMRA All PI Meeting
October 20-22, 2009
Meeting Summary

Purpose/Background

The fourth annual CAMRA All PI meeting was held in Cincinnati, OH at the Kingsgate Hotel and Conference Center and the main offices of the EPA National Homeland Security Research Center (NHSRC). The All PI meeting was shared throughout the EPA via webinar so that those interested parties were given access to information being shared from the PIs and their students and Post-Docs.

The main theme of the meeting was to elaborate on the outputs and outcomes of the work CAMRA has been doing. The presenters also focused on the products which can be used outside of CAMRA. The first night of the meeting focused on the external face of CAMRA which will take the form of a Microbial Risk Assessment Wiki (MRA Wiki) which interested parties will be able to search to learn the most up-to-date information on QMRA. The second day was an all day webinar sharing our knowledge and advancements. The final day allowed for CAMRA PIs and students to discuss further the MRA Wiki and how the different projects will be able to contribute and what would be the best layout and means of distributing the information. The agenda is attached below and followed with a summary of the results from the meeting.

Schedule

NEW KNOWLEDGE INFORMING MICROBIAL RISK ASSESSMENT
Presented by CAMRA an EPA/DHS Center of Excellence
October 20-22, 2009
ALL PI MEETING and WEBINAR

20 October

CAMRA PIs/students: Introductions and overview of key outputs and products.
Presentation of the data warehouse mock-up
Details of the dose response module
Table discussions of data warehouse framework and modules.
Table reporting out and adjournment   4:00 PM – 8:00 PM

NEW KNOWLEDGE INFORMING MICROBIAL RISK ASSESSMENT
Presented by CAMRA an EPA/DHS Center of Excellence
October 21, 2009

Welcome and Introduction
Welcome and Purpose of Meeting   EPA   8:30-8:40 AM
Overview of CAMRA and QMRA frameworks:

The Long term goals, and progress made toward informing microbial risk assessments

                                                              Joan B. Rose   8:40– 9:00 AM

Exposure Detection, Surrogate Development, Fate and Transport of Agents in the Environment

Overview of Surrogates and Survival for Bioterrorist Agents
                                                           Charles Gerba   9:00 – 9:20 AM
Transport of Potential Bioterror Pathogens in Water Distribution Systems
                                                             Pedro Romero   9:20 – 9:40 AM
Transport of *Bacillus anthracis* and other Potential Bioterror Pathogens in Air
                                                       Mark Nicas   9:40 – 10:00 AM

Break   10:00 -10:30 AM

Assessment of Molecular Methods Determination of Detection Limits for *Bacillus anthracis* and Implications for Other Pathogens such as the Influenza Virus
                                              Amanda Herzog   10:30 – 10:50 AM
A Tool for Analyzing Biphasic Nature of Pathogen Dispersion and Survival on Fomites
                                              Patrick Gurian   10:50 – 11:10 AM
Overview of Transfer Efficiencies of Potential Bioterror Agents
                                              Charles Gerba   11:10 – 11:30 AM
Follow up discussion   ALL   11:30 – 11:50 AM
LUNCH   12:00 – 1:00 PM

22 October

EPA feedback   EPA and PI Panel   8:30 – 9:30 AM
Discussion on warehouse

Years 4 and 5 activities
(Pathogen focus: MRSA)   Sidath Gunawardena and or Mark H. Weir
                                              ALL PIs   9:30 - 11:00 AM
Update on Annual Report
Final wrap-up
CAMRA[2] .   EPA and PI Panel   11:00 - 1200 AM

Summary

Tuesday 20 October

Whole-group discussion following Rosina's presentation on the proposed data warehouse (MRA Wiki)

- This is not really meant to be a new or digital version of the purple book
  - More complementary
- May need separate interfaces for experts and novices
  - Learning QMRA section?
- Uncertainties about a more complex interface vs. a more simplified interface-how do you choose the particular area you're interested in?
- MRA Wiki described as living 'IRIS' for microbes; good interface for getting info about particular hazards.
- Importance of uncertainties and how it relates to model choice:
  - Attenuation vs. dose-response: are 3 data points with a dose-response model really worth anything even if the fit appears to be good?
- CDC centers for public health excellence in informatics potential examples:
  - Linking 'omics' databases
  - Should we attempt to fit in to such a framework? Utah's is infectious disease control oriented. PH & medicine fit closely into QMRA.
- Need to start with a 'static' data repository – well structured and thought out, without lots of people randomly entering stuff – participation by other users would have to come later.

Brainstorming over dinner-

Audience
- This is a repository of data for info useful for further models.
- Audience is QMRA modelers; these people are looking for parameters and we need to consider what those people are looking for and how to make it easy for them to find the parameters.
  - This seems like more of a support tool for people to find the data bits they need to formulate models with.
- Precise QMRA framework is still murky and there are multiple valid ideas of it – different frameworks may be valid for different situations, e.g., anthrax is nontransmissible and so transmission models don't apply. But a unified framework may be needed that subsumes the different possible frameworks and points the user toward the 'correct' one (or away from aspects of QMRA that are not necessary for the particular problem).

Interface/output
- The MRA Wiki is useful as a starting point with the Pathogen Safety Data Sheets (PSDS) – more advanced stuff comes later and the MRA Wiki helps users find more detailed info, e.g., by pointing people toward papers or datasets.
- Need to be able to get precise info about particular issues.

General strategy for designing the data warehouse
- Include information about what is known and what is unknown – structured reports help with that because you can see the gaps.
- Framework should be conceptual rather than simply data-driven.
- Need to attain critical mass in a few areas – we have it for dose response, perhaps (uncertainties in dose-response may be greater than commonly realized). If something is diffuse and not yet well-

researched, maybe it shouldn't be in there.
- Need to guard against being too diffuse and concentrate on particular aspects for which we have a lot of info. Might necessitate just doing a database on dose-response rather than QMRA generally, for example. Approach to a particular area needs to be comprehensive – such that it has (nearly) everything known about a particular area.

Back-end structure
- Needs to be a relational database rather than a hierarchical database for more flexible search
- Need information about statistical approaches used to carry out analyses that are fit to data.
- Access to raw data (and its metadata) is essential & most important – after that comes the analyses.

Gaining users by serving users
- We need a good basic and broad framework to get the funding to make a REALLY good product – one road to this might be to make a very specific resource about one aspect of QMRA.
- Could show depth for a subset of pathogens as well as depth in particular subject areas.

Wednesday 21 Oct 11:30 Discussion

- Considerations regarding surrogate organism selection
  - What do we know about which surrogates are important?
- Paper in draft:
  - A framework/protocol that still needs to be evaluated. Need to test how well the protocol works with past surrogates.

Thursday 22 October
Discussion with EPA attendees and CAMRA PIs

- EPA: CAMRA with expertise in water is the only center looking at this and evaluating the risk for this vector.
  - CAMRA:
    - Summer institute project with washdown of surfaces after anthrax release (outdoors) including fate and transport of the spores in the storm water system and Puget Sound.
    - New sensor lab which can connect EPA modeling efforts with CAMRA security work.
    - Possibility of a CAMRA H_2O piece dedicated just to water issues.
- EPA: Regarding water risk communication and perception is very important EPA is getting started with this as well
  - CAMRA:
    - Prior outbreaks are good tools for initial modeling of this.
    - Other issues such as biofilms can be investigated with this concern as well.
  - EPA: Need to give stronger message to congress on this in order to push the point that water is just as important for understanding risk. Perhaps should work together to get this accomplished.
    - CAMRA: There are possible means of accomplishing this that may require further discussion.
      - Polio work thus far and the needs in that area is a good starting point for this as well as the tularemia work done thus far including the data

generated by Dr. Carol Bolin at MSU.
- Recent simulations and other planned studies can give insights onto this as well as a means of proving the point.
- EPA: Multiple dosing studies being planned through EPA as well
  - CAMRA:
    - Perhaps we should discuss how long to progress these studies, perhaps over the phone.
  - EPA:
    - Using acute information to inform the multiple dosing strategy.
- DHS: Work with the chemical and biological division in the Science and Technology Directorate in DHS to connect industry partners and needs that CAMRA can work with. May be able to leverage the technical expertise available to progress CAMRA's and the division's other needs through partnerships. And keep the customer's needs and interests in mind.
- EPA: Interest in pulling work and outputs from CAMRA in order to make the tools available in order to allow others to use the information and tools especially those involved in the decision making process during an emergency situation.
  - CAMRA:
    - The MRA Wiki is one main way that CAMRA can disseminate the information to those most likely to use it.
    - The QMRA framework has changed from the traditional risk assessment framework and this should be shown as well.
  - EPA:
    - If a malicious incident or adverse natural incident occurs decision makers need to be able to use the tools and information practically
  - CAMRA:
    - The MRA Wiki is being designed for practical use so this may alleviate that concern.
    - Exercises already done on anthrax classified or not can be useful if made available.
    - Started influenza rapid response based on risk assessment this may alleviate concerns of not using long range risk estimates and not focusing on casualty estimates or economic impact but actual response options etc. Expanding the XDR TB response as a good starting point.
- EPA: Detection and sampling strategies as well as persistence are other concerns after an event may require work on a bio cleanup protocol which is risk reducing and cost effective.
  - CAMRA:
    - Other options from fumigation may be options since fumigation is not always necessary, costly and not as effective as assumed.
- Facilitator: Integration has been mentioned as important how has work progressed on that
  - CAMRA:
    - Putting key assumptions and needs for the innate immune systems modeling.
  - EPA: Reoccupancy is a chief concern therefore sensitive subpopulations may dictate the more conservative risk estimates. Also setting the correct risk levels based on the sensitive subpopulations.
    - CAMRA
      - Low availability of low dose data will make this difficult especially for pathogens other than Category A
      - Work at Carnegie Mellon with the focused interviews shows value of having a risk level which can be mentioned to the public. Work here also shows that there is not sufficient information to discuss reality of

tradeoffs between money and lives
- DHS: Getting involved in city wide exposure perhaps recommending evacuation of city before deaths occur (i.e. water distribution system attack)
    - CAMRA
        - This type of attack can be particularly scary to the public therefore we need to know how to address the media in this case.
        - Even is water is shipped in there is a large economic impact how do you get enough water for hospitals, businesses such as restaurants will need to temporarily shut down and industry that cannot treat its own water may need to temporarily shut down as well.
        - May look at what earthquake zoned cities have planned for water needs.

Appendix D: Year IV Statement of Tasks

Investigators	Status of Year 4 Tasks for Project I
Charles Gerba Mark Nicas	**Completed** Evaluation B. thuringiensis recovered from fomites-cultivation • Markov model in aircraft cabin (completed)
Amanda Herzog Ryan Sinclair Mark Nicas David Greenburg Christopher Choi Pedro Romero	**In Progress** • Genetic characterization of highly touched and untouched fomites. • Loss due to recovery vs loss due to decreased infectivity of P22 • Quantum dots as surrogates for microorganisms Modeling axial dispersion in laminar pipe flows Contaminant Source Location in water systems with neural network • Survival of viral pathogens on fomites Learning Unit Created on 2009-03-04 16:39:38.0 Transfer efficiencies of bacteriophage and influenza virus • Markov model of particle fate and transport in aircraft cabin • Tranfersability of organisms from fomite to hand Review of transfer of orgnisms from fomites to human skin • Testing the surface-to-hand dose predictions of exposure model • Developments in experiments on droplet spray exposure. • Ecological assessment of *B. anthracis* strain survival Advances made in unit 135 • Multiobjective Sensor Optimization in Water Distribution Systems Experimental verification of axial dispersion in laminar flows • Single-objective sensor optimization in potable water systems.

Investigators	Status of Year 4 Tasks for Project II
Joeseph Eisenberg and Ian Spicknall Joeseph Eisenberg and Ian Spicknall	**Completed** • Dominant Routes of Influenza Transmission in Different Contexts QMRA Summer Institute Influenza Case Study **In Progress** • Assessing intervention effects in variable influenza contexts ODE Model and Analysis of the Dominance of Influenza Routes

Investigators	Status of Year 4 Tasks for Project III
Sharon Nappier	**Completed** • Equine Encephalitis Virus Dose Response Models
Sushil Tamrakar	• Data sets used in modeling dose-response for Lassa virus
Mark H. Weir	• Development of Physiologically Based Dose Response Models • Dissertation: Incorporating time to response into dose-response
Toru Watanabe	• Dose-response model for influenza A virus
Toru Watanabe	**In Progress** • Dose-response model for influenza A virus
Sushil Tamrakar	• Dose-Response Model for Coxiella burnetii (Q fever) • A QMRA Model for Rickettsial Diseases
Sharon Nappier	• Equine Encephalitis Dose Response • Equine Encephalitis Virus - Dose Response Models • R code for Equine Encephalitis Viruses Dose Response Models • Equine Encephalitis Data Files
Mark H. Weir	• Dissertation: Incorporating time to response into dose-response • Development of Physiologically Based Dose Response Models
Yin Huang	• Modeling the effect of multiple doses of scrapie agent • Modeling the effect of multiple doses of Francisella tularensis

Investigators	Status of Year 4 Tasks for Project IV
Tao Hong	**Completed** • Integrated Transport and Risk Model • Identifying sampling strategies
Elizabeth Casman	• Plague equilibria in urban rat populations • Expert model of flu transmission • Draft Report on Valuing Environmental Detection of *B. anthracis*
Patrick Gurian	• Summer Institute Report on Influenza Control • Persistence model selection spreadsheet • Cryptosporidium dose response
Jade Mitchell-Blackwood	• Bayesian Analysis of Historic U.S. Army Data
Tao Hong	**In Progress** • Integrated Transport and Risk Model • Identifying sampling strategies
Elizabeth Casman	• Analyzing Interview Responses for Mental Models Study • Plague equilibria in urban rat populations • Designing and conducting mental models study • Valuing Environmental Detection of *Bacillus Anthracis* •
Patrick Gurian	• Persistence Model Estimation and Selection • Cost-effectiveness of Influenza Control • Cryptosporidium boil water threshold risk
Jade Mitchell-Blackwood	• Hierarchical Modeling of Dose Response Variability

Appendix E: CAMRA Expenditures

CAMRA was established in September, 2005 and was operating by February, 2006. The delay in start up was due to the initial agreements and development of the 6 sub-awards between MSU and each university; Drexel, Carnegie Mellon University, Northern Arizona University, University of Arizona, University of California Berkeley, and University of Michigan. The development and approval of the Quality Assurance Project Plans for each PI after the first All PI meeting at Drexel University in February, 2006 was then begun immediately and progressed though-out the first part of that year.

CAMRA is a 10 million dollar center. Funding was received in the following increments at MSU.

Original Grant Funded	1/31/2006	$2,025,000
Mod 1	1/31/2007	$2,000,000
Mod 2 & 3	2/12/2009	$4,029,500
Mod 4 - from EPA	8/24/2009	$1,000,000
TOTAL		$9,054,500

Years 1-4 funds were distributed to each of the universities along with statement of tasks generally between March and June. For Year 5 funding the half from DHS ($1,000,000) has been received and has been set aside to match to EPA funding in 2010 ($945,500).

Several delays impacted CAMRA funding. The first was making sure all the agreements in place between MSU and the other universities were in agreement with the universities legal requirements. MSU worked diligently and processed the initial 6 sub-awards in 5 months. There was a lag in spending and setting up research programs as a result of the development and approvals of all QAPPs by Dr. Rose and Dr. Haas, while this went smoothly, it did take time. There has been the normal loss of post-doctoral scientists and students that occur has they take on other activities that has delayed some of the project teams who have had to make new hires. This is usual for universities. Project V had some delay in operationalizing KR v2, but it is now serving CAMRA as a repository for our outputs and experimental designs. Unfortunately due to illness, Dr. Bolin has suspended her work until next summer (part of Project III). Due to the nature of these animal experiments, the use of a BL3 laboratory and the special expertise and approvals needed for the technical staff, there is no other group that can undertake the animal-dose experiments. Thus these experiments will be delayed.

Despite these small delays, CAMRA's productivity is reaching a high level and it is anticipated that this output will continue. We anticipate requesting a two year no-cost extension next year due to these delays. This will allow CAMRA to finish the animal experiments, finalize the integrated QMRA outputs and complete the MicrobialRisk.Info (MRI) Wiki which will serve as our Data warehouse.

Figure 1 shows the amount spent as of October, 2009 as recorded at MSU and Fig 2 shows the distribution of funds by project.

	With Pending Total Spent
Drexel University	$1,115,412.46
Carnegie Mellon University	$168,538.74
University of Arizona	$613,222.30
Northern Arizona University	$283,511.62
UC Berkeley	$500,222.41
University of Michigan	$1,064,829.38
Michigan State University	$1,347,706.67
	$5,093,443.58

Figure 1. Total Spent with Pending
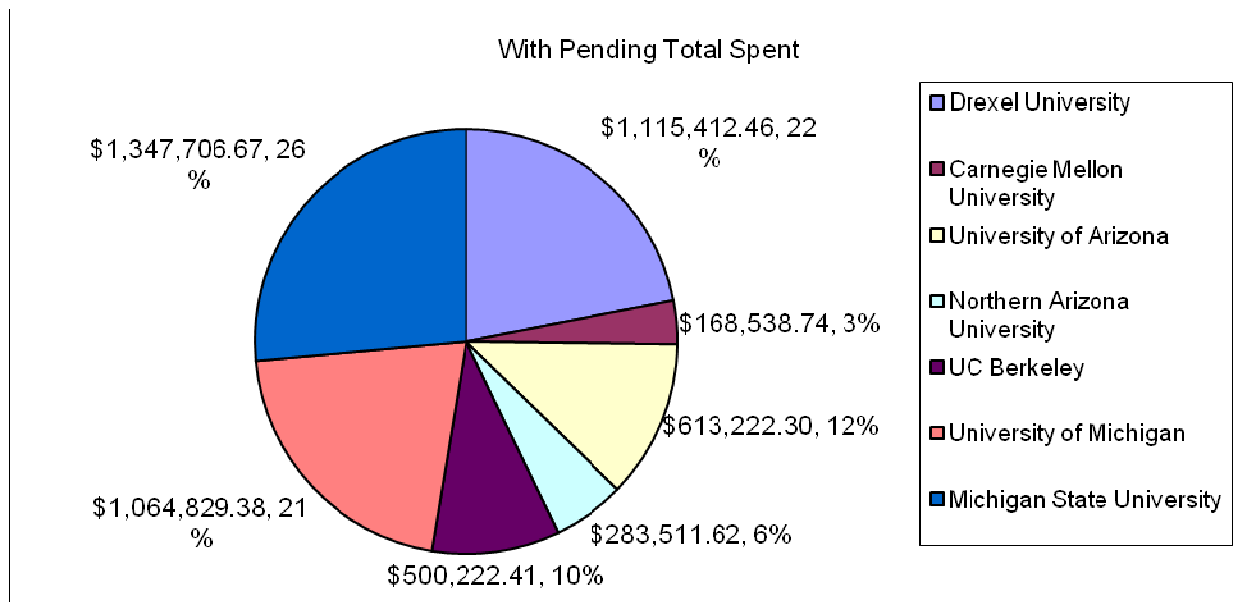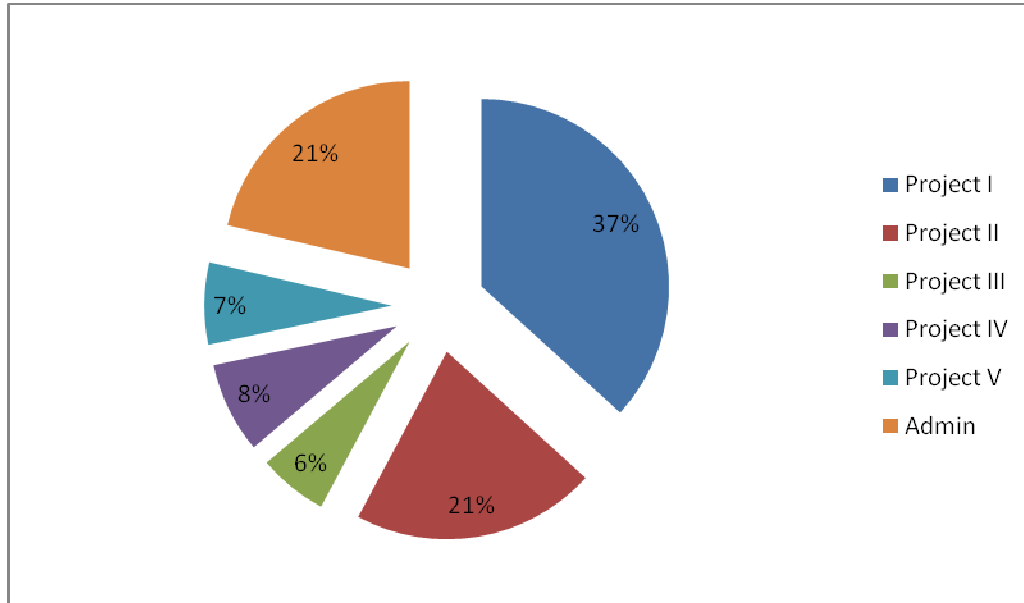
Figure 2. Distribution of Spent Funds by Project

PI	School
Project I	
Gerba	AZ
Choi	
Nicas	UCB
Hashsham	MSU
Wagner	NAU
Project II	
Koopman	UM
Eisenberg	UM
Project III	
Haas	Drexel
Bolin	MSU
Project IV	
Gurian	Drexel
Casman	CMU
Project V	
Weber	Drexel
Admin	
Haas	Drexel
Rose	MSU

Appendix F: QA Report by Rebecca Ives

QUALITY ASSURANCE REPORT

Center for Advancing Microbial Risk Assessment
Year-4

Submitted by
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And

Dr. Matthew Clark
Department of Homeland Security (DHS)
Washington DC

November 27, 2009 report

Background

According to the Quality Management Plan of the Center for Advancing Microbial Risk Assessment (CAMRA), each of the projects was to develop and implement a quality assurance project plan (QAPP) addressing the major elements contained in EPA guidance document, EPA QA/G-5 "Guidance for Quality Assurance Project Plans." With the exception of projects 2 and 5, the projects are subdivided by task among principal investigators. As a result, all projects except project 2 and 5 have multiple QAPPs covering the responsibilities and research objectives under the management of the principal investigator. The QAPPs have been given a numerical designation for organizational purposes. Each principal investigator is either the quality assurance manager for that location/task, or has designated personnel to act in that capacity. Projects described in QAPP P1Q5 and QAPP P3Q8 will not have an updated QAPP for Year 4. The future progress of Project 1 described in QAPP P1Q5 is currently under discussion with the lead PI and the CAMRA co-directors. If work continues under QAPP P1Q5, it will be conducted in Year 5. The section of Project 3 described in QAPP P3Q8 will not be conducting work during Year 4

QAPP P1Q1 and P2Q6 have been delayed. QAPP P1Q5 has been placed on hold. All other final QAPPs were reviewed and accepted by the quality assurance officer, Rebecca Ives and approved by the CAMRA Directors by November 2009.

TABLE A

Project	QAPP #	PI	University	Current QAPP Title & Version	Date QAPP Submitted to QAO	Comments made by QAO* and returned to PI	Date QAPP Approved by QAO	Date approved by CAMRA directors	Date Uploaded to EPA portal	Comments made by EPA and returned to CAMRA
I	1	Chuck Gerba	AZ	QAPP P1Q1 Gerba v4_0.doc						
I	2	Chris Choi	AZ	QAPP P1Q2 Choi v4_0.doc	**10/12/09**	**10/14/09**	**10/29/09**	**11/16/09**		
I	3	Syed Hashsham	MSU	QAPP P1Q3 Hashsham v4_0.doc	**10/12/09**	**10/14/09**	**10/30/09**			
I	4	Mark Nicas	UC Berkeley	QAPP P1Q4 Nicas v4_0.doc	**10/27/2009**	**10/28/09**	**10/29/09**	**11/16/09**		
I	5	David Wagner	NAU	QAPP P1Q5 Wagner v4_0.doc	**N/A**					
II	6	Joe Eisenberg	UM	QAPP P2Q6 Eisenberg v4_0.doc						
III	7	Chuck Haas	Drexel	QAPP P3Q7 Haas v4_0.doc	**10/18/09**	**10/18/09**	**10/28/09**			
III	8	Carole Bolin	MSU	QAPP P3Q8 Bolin v4_0.doc	**N/A**					-
IV	9	Patrick Gurian	Drexel	QAPP P4Q9 Gurian v4_0.doc	**11/19/209**	**11/20/09**	**11/20/09**			
IV	10	Liz Casman	CMU	QAPP P4Q10 Casman v4_0.doc	**10/14/09**	**10/14/09**	**10/14/09**			
V	11	Rosina Weber	Drexel	QAPP P5Q11 Weber v4_0.doc	**10/15/09**	**10/18/09**	**11/19/09**			

*Date of last set of comments

QAPP review findings

P1 Q1: Delayed. Review pending.

P1Q2:
The QAPP has been expanded to include additional outputs and tasks. Additional SOPs and quality objectives and quality criteria have been added as a result. As work has progressed, no major changes to previous quality objectives and quality criteria have been necessary.

P1Q3:
This project is preparing to shift from analysis of data in scientific literature to benchwork experiments. Experimental design for this benchwork is in progress. Additional SOPs and quality objectives and quality criteria will be required as a result.

P1Q4:
Particle release experiments have been completed and project has moved on to the Droplet Spray Exposure Experiments. As work has progressed, no major changes to previous quality objectives and quality criteria have been necessary.

P1Q5: Not conducting work in Year 4. No QAPP update was required for Year 4.

P2Q6: Delayed. Review pending.

P3Q7:
The QAPP has been expanded to include category B agents in the reviewed reference sets of dose-response relationships. As work has progressed, no major changes to previous quality objectives and quality criteria have been necessary.

P3Q8: Not conducting work in Year 4. No QAPP update was required for Year 4.

P4Q9:
Model methods documentation has proven to be unwieldy as a QA/QC tool. Project personnel are switching QA/QC to a checklist that has been in use as part of the model documentation. The checklist is being expanded to accommodate model verification.

P4Q10: Work is proceeding according to the timeline described in the QAPP.   No additional objectives have been added. No revisions were needed in the QAPP update.

P5Q11: Work on the Knowledge Repository (KR) version 1 has completed. Testing has begun on KR version 2. No major changes in quality objectives/ criteria occurred between Year 3 and Year 4. Planning has begun for the Data Warehouse, which will likely require additional quality objectives/ criteria for Year 5.

Audits

By January 2010, each QAM except Dr Casman, Dr Bolin, and Dr Wagner will receive a site visit by the QAO to conduct a technical audit. Dr. Casman conducted a self audit using a checklist provided by the QAO. All audited projects will receive a list of items to address, based on responses to items in a checklist. The quality managers are asked to respond to each item in writing.   Both documents from every audit are archived by the QAO, along with notes and supporting materials collected from project personnel.

Project	University	Lead PI	QA manager	**2009 Audit dates**	QAPP #
I	AZ	Dr. Charles Gerba	Dr. Gerba		P1Q1
I	AZ	Dr. Chris Choi	Dr. Choi		P1Q2
I	MSU	Dr. Syed Hashsham	Dr. Hashsham	11/20/2009	P1Q3
I	UCBerkeley	Dr. Mark Nicas	Dr. Nicas		P1Q4
I	NAU	Dr. David Wagner	Dr. Wagner	NA	P1Q5
II	UM	Dr. James Koopman	Dr. Eisenberg / Dr Koopman		P2Q6
III	Drexel	Dr. Charles N. Haas	Sushil Tamrakar		P3Q7
III	MSU	Dr. Carole Bolin	Dr. Bolin	N/A	P3Q8
IV	Drexel	Dr. Patrick Gurian	Dr. Gurian		P4Q9
IV	CMU	Dr. Elizabeth Casman	Dr. Casman	10/30/2009	P4Q10
V	Drexel	Dr. Rosina Weber	Dr. Weber		P5Q11

Audit Findings:
P1Q3: Laboratory work is progressing on schedule, although there have been delays in publications. The audit noted that servicing for the balance was overdue, however as this is only used for media production, this deviation is not likely to impact the work quality. Positive media controls indicate acceptable media performance. The audit noted damage to the pH probe occurring as a result of a common key for all labs located in the ERC building, which allows access to personnel unfamiliar with the equipment. This open access and resulting damage has the potential to interrupt work. Project personnel are investigating changing locks on the laboratory door to restrict access or purchase of a probe for the project that will be stored in a locked cabinet when not in use.   The audit noted a lack of documentation of the oversight of project personnel by the QAM.

P4Q11:
QAPP is closely followed, no changes were requested by the QAO.

Quality Assurance Report Update: An update to the Quality Assurance Report will be prepared after completion of the audits.