**Center for Advancing Microbial Risk Assessment
Year-3 Annual Report**

Submitted to

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November 26, 2008

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5-page Summary Annual Report

Center for Advancing Microbial Risk Assessment (CAMRA)
EPA Agreement: RD832262
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Introduction:

Infectious diseases such as influenza, norovirus, tuberculosis, and antibiotic resistant *Staphlococcus* are causing major concerns for hospitals, nursing homes, schools, airlines and the public at large. Recent events have increased awareness of potential vulnerabilities to widespread disease outbreaks. The 2003 SARS epidemic has brought new attention to zoonotic diseases like Bird Flu, while Hurricanes Katrina and Rita have brought attention to environmental contamination. The relationships between climate change, emerging illnesses associated with storms, and aging infrastructure are important areas where national security strategies are needed and are being developed. In the post 9/11 world, national security requires us to address the possibility of another bio-terrorist attack like the anthrax attacks of 2001. Advances in environmental diagnostics are required to better evaluate environmental contamination and clean up goals. The Biowatch program is an example of the vigilance required to detect bio-terror attacks. Biowatch continues to monitor the outdoor and now the indoor environment, and has been able to identify hoaxes, such as the powder recently found at the University of Michigan athletic facility.

CAMRA was established in September, 2005, with two major goals: advancing 1) the technical science of and 2) the knowledge management for microbial risk assessment. This is the only Center of Excellence which is addressing and developing the technical information, models and tools necessary for quantitative microbial risk assessment (QMRA). CAMRA is modifying the National Academy of Science chemical risk assessment framework to address infectious agents and provide evidence-based science for the development of sound policies by regulatory agencies like EPA, DHS, and others. CAMRA has established four of its research projects around 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.
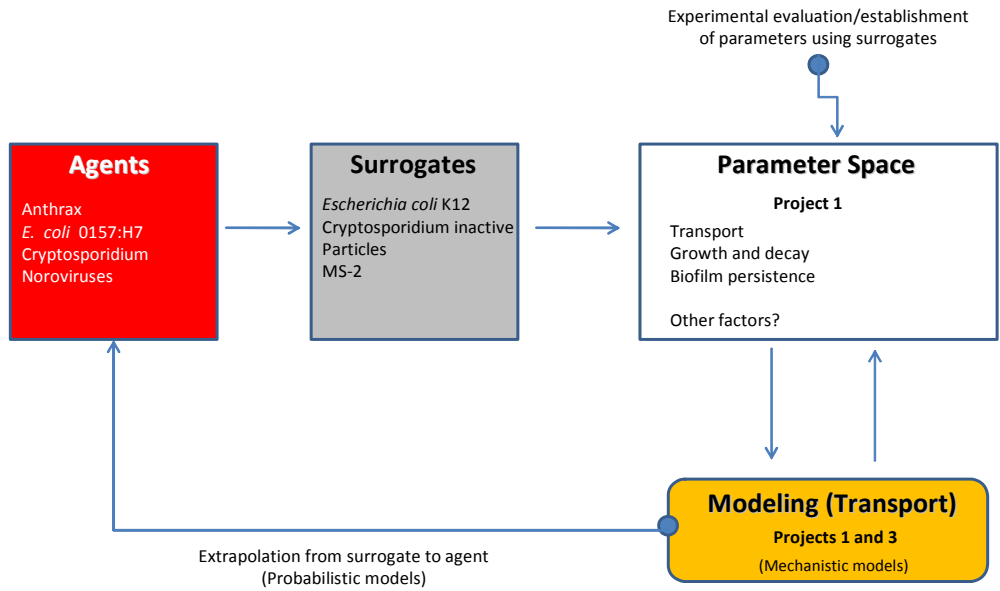
EPA, DHS and other agencies (CDC, USDA, and state agencies) are developing policies for environmental monitoring and clean up after natural disasters or terrorist attacks. In three years, CAMRA has developed a new infectious disease transmission paradigm, new dose-response models for all the class A agents, key information that addresses pathogen survival and transmission via the indoor environment (including fomites), and new models of risk in water distribution systems. This work is addressing critical scientific gaps in several areas that are needed to protect the nation against infectious diseases.

The inability to judge microbial risks with a "quantitative" yard stick has been a major limitation for managing microbial threats. CAMRA is providing this yard stick by providing information on exposure (including survival of important pathogens) and connecting it with dose-response models, which can be used for threat ranking by everyone from first responders to risk assessors to remediation engineers. CAMRA has begun to reveal the details of two important exposure pathways (Figure 1). The water exposure route focuses on survival, fate, and transport of biological agents of concern (BAC) within a water distribution system. It is clear that water distribution systems are vulnerable to contamination, can spread disease to a large population, and are difficult to monitor and clean up. The second pathway is associated with the air exposure route in indoor environments and deals with the survival, fate, and transport of BAC both in aerosols and on fomites, requiring dose-response information for both inhalation
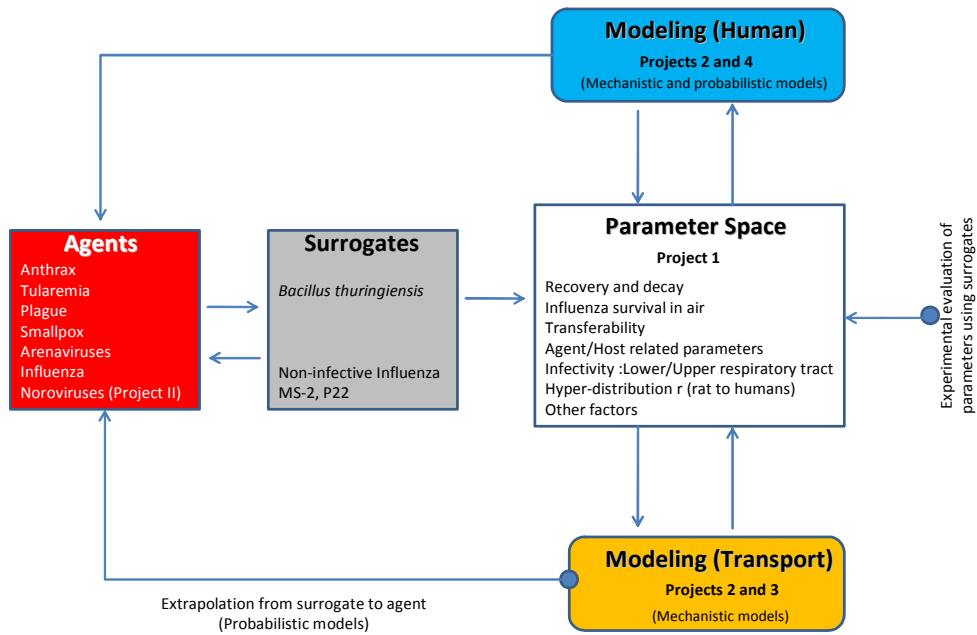
and ingestion by hand-to-mouth transfer from fomites. The air exposure route includes person-to-person disease transmission and thus integrates human behavior into the risk assessment.

Integrating Frameworks

Water Exposure Route

Experimental evaluation/establishment of parameters using surrogates

Agents

Anthrax
E. coli 0157:H7
Cryptosporidium
Noroviruses

Surrogates

Escherichia coli K12
Cryptosporidium inactive
Particles
MS-2

Parameter Space

Project 1

Transport
Growth and decay
Biofilm persistence

Other factors?

Modeling (Transport)

Projects 1 and 3

(Mechanistic models)

Extrapolation from surrogate to agent
(Probabilistic models)

Air Exposure Route

Modeling (Human)

Projects 2 and 4
(Mechanistic and probabilistic models)

Agents
Anthrax
Tularemia
Plague
Smallpox
Arenaviruses
Influenza
Noroviruses (Project II)

Surrogates

Bacillus thuringiensis

Non-infective Influenza
MS-2, P22

Parameter Space

Project 1

Recovery and decay
Influenza survival in air
Transferability
Agent/Host related parameters
Infectivity :Lower/Upper respiratory tract
Hyper-distribution r (rat to humans)
Other factors

Experimental evaluation of parameters using surrogates

Modeling (Transport)

Projects 2 and 3

(Mechanistic models)

Extrapolation from surrogate to agent
(Probabilistic models)

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CAMRA Project I has published the normalized decay rates for viruses and class A agents on fomites which allows for the prediction of the survival on common indoor fomites. This can be used in models to assess the risk of infection to first responders or other exposed individuals after the release of an agent of concern in buildings. We have found that the decay occurs quickly in the first few hours due to drying, particularly of the bioaerosol droplets on the surface.

Project II has shown that incorporating the environment into the models results in slower infection transmission dynamics in epidemics than those predicted by deterministic models without the environment. They have found that the frequency with which fomites are touched by different individuals can markedly alter the effects of numbers of people at a venue on infection spread. Touching frequency is thus a key issue to be addressed in setting cleanup priorities. Additionally they have shown that probability of infection might depend not only on the dose but also in the time of exposure. They have accordingly developed models to help address how timing alters infection risks and cleanup criteria and they have helped design experiments to quantify these dose-timing effects. Dose-timing effects could determine whether transmission by air or fomites is more important. We found that the efficacy of intervention depends on the coverage as well as contact patterns between individuals.

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, and has addressed *Francisella tularensis* associated with ingestion and multiple exposures. This is the first multiple exposure experiment undertaken. Dose-response for XDR (drug resistant TB) was also investigated. 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 this information and develop decision science based approaches for determining the safety level focusing on Anthrax

CAMRA developed a rapid alert associated with the risk of TB transmission by an infected individual during air travel for EPA and CDC. The risk estimate with a CAMRA Alert was facilitated by the CAMRA Co-Directors Rose and Haas together with Dr. Nicas, Dr. Masago, Ms. Jones and Dr. Bartrand. This work has been accepted for publication in *Risk Analysis.*

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

The greatest uncertainty in assessing the risk from microbial agents is in predicting the exposure to the agent in a given environment (building, drinking water). Project II activities are designed not only 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.

- Existing data on the survival of bio-threat agents in air, fomites and water were analyzed and survival constants developed which are used to predict die-off rates for these agents.
- Studies involving bio-threat agents and surrogates were conducted to develop a model for better prediction of bio-threat agents on fomites. A workshop for project I, II and III identified critical data gaps including 1) shedding rates of agents by infected individuals, 2) survival of agents on the skin and cloth 3) type of activity in a given building, 4) population density, 5) transfer of the organism from hand to fomite and from fomite to hand, and 6) frequency of fomite and face contact. We began addressing these data gaps in year 3, and will continue through years 4 and 5. Data collected from a norovirus outbreak of gastroenteritis was used to demonstrate the plausibility of our fomite risk model to predict attack rates.
- The detection limits and other limitations (false positive and false negative rates) of analytical methods used for *Bacillus anthracis* were quantified through a literature review and laboratory assessment. It was found that most method groups do not address environmental limits of detection, which is needed for QMRA models.

Assessing exposure via drinking water from intentional releases of bio-threat agents requires an understanding of the dispersion of these agents. Such information can also be used to determine where an

agent was released into a distribution system. Using a model distribution system, the axial dispersion of a virus, a bacterium, and a spore have been modeled. These studies indicate significant retardation of microbes with long tailing effects of the organism in the water after release. Experimental data in small-scale pipe networks were used to better refine existing mixing models for contaminants in distribution systems to allow for predicting concentrations of bio-threat agents within large scale complex drinking water distribution systems.

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

We have made the crucial first steps in the analysis of infection transmission through the environment from person to person. We are now on the path to developing the first methods that will allow us to determine exactly where and how infection is being transmitted, how each mode of transmission fits into the overall transmission system, and how much we can expect from efforts to interrupt environmental transmission paths. We have created a theoretical framework that can be elaborated toward these ends and we have identified the measurements that will advance them. Our theoretical framework is a series of models that range from the conceptually abstract to highly parameterized simulations of reality. These can inform each other and point the way to the most informative research. They include an environmental infection transmission system model (EITS), realistic venue simulations of transmission (RVST), and cumulative dose response models (CDRM). The EITS have taught us that the frequency with which different individuals touch objects is a crucial distinction models must address and that the probability structure affecting the chances of an outbreak can be influenced by environmental transmission. This provides guideposts for RVST development. The RVST have taught us that in addition to environmental parameters, characteristics of human movement and social structure at venues can affect the route of transmission that is realized. The CDRM have taught us that different patterns of timing through which airborne and fomite spread transmission reach an individual can alter the risk of transmission. We have developed simplifications of our CDRM that allow these models to be integrated into the RVST.

Project III: Dose-response Modeling and Application

We have conducted a large number of reviews of dose response relationships for pathogens of concern. Many of these have been published, submitted for publication, or presented at meetings. These relationships describe how the risk of an adverse event varies with the dose of an infectious agent. These relationships can be used in several fashions:

- In the event of a release of an agent, the risk to the population from the exposure (based on exposure estimates from Project I) can be computed.
- The residual concentration of an agent after remediation from an incident can be used to compute a residual risk, and in conjunction with work from Project IV can be used to assess the appropriate level of response to an incident.

The developed dose response models and refinements include: *Bacillus anthracis*, *Variola major*, *Yersinia pestis*, *Burkholderia pseudomallei*, *Burkholderia mallei*, *Francisella tularensis*, *Mycobacterium tuberculosis* and the Lassa hemorrhagic fever virus.

We have also been working to incorporate time since exposure into dose-response modeling, which will enable an estimation of when adverse effects are expected following dosing. This work, to date, has analyzed dose-time models for *Yersinia pestis*, *Francisella tularensis* and *Mycobacterium tuberculosis*. Also Project III is the first to include the age of the host as a modifier for the infectivity of *Variola major* into microbial dose response models.

The Project III team at Drexel is working with the Project III team at Michigan State to obtain new experimental data on the response of animals to ingestion of *Francisella tularensis* which will be used for the development of improved dose response time models. By comparison of the experimental data with literature data on inhalation dose response, we hope to better inform extrapolation of risks between different portals of entry.

Project IV: Assessment-Analysis Interface

The integrated fate, transport, and health risk model developed in the previous year was used to calculate surface concentrations corresponding to different risk levels. If risk managers identify what acceptable risk levels are for anthrax, then these relationships can be used to develop non-zero standards for re-occupancy of contaminated buildings. A sensitivity analysis was conducted to identify the factors that contribute the most to uncertainty in these concentrations, so that future work can focus on the most important uncertainties.

A related effort,examined possible definitions of acceptable risk for anthrax from a benefit-cost perspective. A decision model was developed analyzing the net benefits of prophylactic antibiotic treatment as a function of risk of contracting anthrax. A risk level was found at which the net benefits of treatment were offset by the monetary costs and possibility of side effects due to treatment. The level of risk may be considered "acceptable" in that preventative action would be expected to produce negative net benefits (i.e., at this level one would prefer to accept the anthrax risk rather than take a more dangerous action to reduce it). While benefit-cost considerations are only one of the many factors that drive societal determinations of acceptable risk, such analyses may help to inform the decision making process for remediation standards and other response actions.

A third effort conducted in collaboration with Project III developed risk-based targets for ambient air monitoring. The project combined the latest dose-response functions developed by Project III researchers with a decision model of allowable risk to estimate air sampling rates required to detect various levels of health risk due to three Category A agents: *B. anthracis*, *Y. Pestis*, and Lassa virus. This work can guide the design of ambient monitoring programs and the interpretation of the results of such programs.

Project V: Knowledge Management, Learning and Discover

The KM version 2 is now operating and in October, 2008, PIs began updating learning units and accomplishments.   Project V is now exploring the terms and the language of QMRA. KM v2 will be searchable and will begin to form the basis of the final CAMRA data warehouse. This warehouse is now under development.

Specific Accomplishments for Year 3

As of 11/25/2008 (Based on KR and all submitted reports)

- Peer Reviewed Publications   19
- Peer Reviewed Proceedings   3
- Book Chapters   1
- Master's Theses   2
- PhD Dissertations   1
- Un-refereed Documents   6
- Conference Presentations   46
- Other Presentations   1
- Workshops   3
  - 2008 QMRA Summer Institute
    - 30 participants (24 academic, 6 government)
    - 5 nations (Australia, Brazil, Canada, United States, Venezuela)
- Students Supported   12
- Students Graduated   3
- Year 3 Learning Units Completed   38
- Year 3 Learning Units In Progress   23

Appendix A: Summary of Accomplishments

Publications
(Peer reviewed journals)

1. Sinclair, R., S. A. Boone, D. Greenberg, P. Keim, and C. P. Gerba. 2008. Persistence of Category A select agents in the environment. Appl. Environ. Microbiol. 74:555-563.
2. Romero-Gomez, P., C. K. Ho, and C. Y. Choi. 2008. Mixing at Cross Junctions in Water Distribution Systems – Part I. A Numerical Study. ASCE Journal of Water Resources Planning and Management 134(3):284-294.
3. Austin, R. G., B. van Bloemen Waanders, S. McKenna and C. Y. Choi. 2008. Mixing at Cross Junctions in Water Distribution Systems – Part II. An Experimental Study. ASCE Journal of Water Resources Planning and Management 134(3):295-302.
4. Masago, Y., T. Shibata, and J. B. Rose. 2008. Bacteriophage P22 and Staphylococcus aureus Attenuation on Nonporous Fomites as Determined by Plate Assay and Quantitative PCR. Applied and Environmental Microbiology 74(18):5838-5840.
5. Bartrand, T. A., M. H. Weir, and C. N. Haas. 2008. Dose-Response Models for Inhalation of *Bacillus anthracis* Spores: Interspecies Comparisons. Risk Analysis 28(4):1115-1124.
6. Tamrakar, S.B. and C. N. Haas. 2008. Dose-Response Model for Lassa Virus. Human and Ecological Risk Assessment 14(4): 742-752.
7. Tamrakar, S.B. and C. N. Haas. 2008. Dose-Response Model for *Burkholderia pseudomallei* (melioidosis). Journal of Applied Microbiology 105(5):1361-1371.
8. Casman, E. A. and B. Fischhoff. 2008. Risk Communication Planning for the Aftermath of a Plague Bioattack. Risk Analysis 28(5): 1327-1342.
9. Ryan, G. G. Sinclair, C. Y. Choi, M. R. Riley and C. P. Gerba. 2009. Pathogen surveillance through monitoring of sewer systems. Adv. Appl. Microbiol. 65:249-269 (In press).
10. Jones, R.M., Y. Masago, T. A. Bartrand, C. N. Haas, M. Nicas, and J.B. Rose. Characterizing the Risk of Infection from *Mycobacterium tuberculosis* in Commercial Passenger Aircraft using Quantitative Microbial Risk Assessment. Risk Analysis (In press).
11. Choi, C. Y., I. Song, and P. Romero-Gomez. Solute Transport in a Pressurized Pipe Network with Multiple Cross Junctions. ASCE Journal of Hydraulic Engineering (Currently under Review).
12. Pujol, J. M., J. E. Eisenberg, C. N. Haas, and J. S. Koopman. The Effect of Ongoing Exposure Dynamics in Dose Response Relationships. PLoS Computational Biology (Currently under Review).
13. Eisenberg, J. E. A Dynamic Dose-Response Model for Modeling Infection Transmission. Journal of the Royal Society Interface (Currently under Review).
14. Li, S. Dynamics and Control of Infections Transmitted from Person to Person Through the Environment. American Journal of Epidemiology (Currently under Review).
15. Weir, M. H. and C. N. Haas. Quantification of the Effects of Age on the Dose Response of *Variola major* in Suckling Mice. Human and Ecological Risk Assessment (Currently under Review).
16. Huang, Y., T. A. Bartrand, and C. N. Haas. Incorporating time post inoculation into a dose response model for *Yersinia pestis* in mice. Journal of Applied Microbiology (Currently under Review).

17. Huang, Y. and C. N. Haas. Time-to-dose-response Models for Microbial Risk Assessment. Risk Analysis (Currently under Review).
18. Huang, Y., T. Hong, T. Bartrand, P. L. Gurian, C. N. Haas, R. Liu, and S. Tamrakar. How Sensitive is Safe? Risk-based Targets for Ambient Monitoring of Pathogens. IEEE Sensors Journal (Currently under Review).
19. Durham, D. and E. Casman. Threshold Conditions for Bubonic Plague Persistence in Urban Rats. PNAS (Currently under Review).

(Peer Reviewed Proceedings)
1. Weber, R. O., S. Gunawardena, and C. MacDonald. 2008. Horizontal Case Representation. In: Advances in Case-Based Reasoning: Proceedings of the European Conference on Case-Based Reasoning. Althoff, K.-D., R. Bergmann, M. Minor, and A. Hanft, eds. pp. 548-561. Springer, Berlin / Heidelberg.
2. Weber, R. O. and S. Gunawardena. 2008. Designing Multifunctional Knowledge Management Systems. Proceedings of the 41st Annual Hawaii International Conference on System Sciences (HICSS-41):368-377.
3. Weber, R. O., S. Gunawardena, and G. Abraham 2008. Representing and Retrieving Knowledge Artifacts. In: Proceedings of the 7th International Conference on Practical Aspects of Knowledge Management (PAKM). T. Yamagchi ed. pp. 86-97. Springer-Verlag, Berlin / Heidelberg (In press).

(Book Chapters)
1. Pepper, I. L., C. Y. Choi, and C. P. Gerba. Microorganisms and bioterrorism. In: Environmental Microbiology. R. M. Maier, I. L. Pepper and C. P. Gerba, eds. pp. 565-574. Academic Press, San Diego.

(Theses / Dissertations)
1. Henley, J. B. 2008. Thesis for Master of Science. Determining the Inactivation Rates of Viruses on Indoor Surfaces. College of Agriculture and Life Sciences, Department of Soil, Water, and Environmental Science, University of Arizona.
2. Herzog, A. 2008. Thesis for Master of Engineering. Factors to Consider in the Evaluation of Risk at the Environmental Detection Limit. Center for Microbial Ecology, Department of Civil and Environmental Engineering, Michigan State University
3. Jones, R. M. 2008. Dissertation for Doctor of Philosophy. Experimental Evaluation of a Markov Model of Contamination Transport in Indoor Experiments with Application to Tuberculosis Transmission in Commercial Passenger Aircraft. School of Public Health, Division of Environmental Health Sciences, University of California, Berkeley.

(Un-refereed documents)
1. Masago, Y, Jones, R, Bartrand, TA, Haas, CN, Rose, JB. 2008. Estimates of risk associated with a tuberculosis patient and air travel. CAMRA TB Alert Report.
2. Rose, J. B., C. N. Haas, P. L. Gurian, and J. S. Koopman. 2008. *Instruction manual for quantitative microbial risk assessment (QMRA)*. CAMRA 3rd QMRA Summer Institute, Michigan State University, East Lansing, MI.
3. Herzog, A., C. Rodriguez, K. Enger, M. Milbrath, O. Bucher, P. Okelo, S. Luster-Teasley, and Y. Huang. 2008. Risk Assessment on Anthrax release in IRS Building. Group A Case

Study: CAMRA 3rd QMRA Summer Institute, Michigan State University, East Lansing, MI.

4. Pandey, A., W. Betacourt, A. Baynton, A. Wright, K. Bush, S. Khan, K. Shaw, A. Coulliette. 2008. Adventure Vacations: Leaving Norovirus at the Dock: A QMRA Assessment of Norovirus Outbreaks on Houseboats. Group B Case Study: CAMRA 3rd QMRA Summer Institute, Michigan State University, East Lansing, MI.

5. Mendoza-Sanchez, I., F. Simmons, C. O'Donnell, M. Sato, A. Rajić, B. Mayer, A. Jenkins, J. B. Rose, and G. Medema. Tularemia in Water: A Quantitative Microbial Risk Assessment. Group C Case Study: CAMRA 3rd QMRA Summer Institute, Michigan State University, East Lansing, MI.

6. Gurian, P., I. Young, M. T. Pepe Razzolini, R. Johnson, B. Schmidt, C. Flemming, T. Hong, and A. Smith. Risk Assessment for H5N1 Influenza A: Border Inspection of Smuggled Goods Exposure. Group D Case Study: CAMRA 3rd QMRA Summer Institute, Michigan State University, East Lansing, MI.

Presentations
(Conference)

1. Henley, J. B. and C. P. Gerba. 2008. Determining the inactivation of viruses on fomites. Ann. Mtg. 108th American Society for Microbiology (ASM) General Meeting, Boston, MA, June 2008.

2. Sinclair, R. G. G., C. P. Gerba and C. Y. Choi. 2008. Axial dispersion of salt tracers and MS-2 phage in an experimental water distribution system. 108th American Society for Microbiology (ASM) General Meeting, Boston, MA, June 2008.

3. Choi, C. Y. and I. L. Pepper. Recent Advances in Water Quality Modelling in a Pressurized Pipe Network. Singapore Water Week Convention, June 24, 2008.

4. Choi, C. Y., J. Y. Shen, and R. G. Austin. Development of a Comprehensive Solute Mixing Model (AZRED) for Double-Tee, Cross, and Wye Junctions. 10th Annual Water Distribution Systems Analysis Symposium, South Africa, August 19, 2008.

5. Romero-Gomez, P., Z. Li, C. Y. Choi, S.G. Buchberger, K.E. Lansey, and V.T. Tzatchkov. Axial Dispersion in Pressurized Pipe under Various Flow Conditions (*Best Paper Award*). 10th Annual Water Distribution Systems Analysis Symposium, South Africa, August 19, 2008.

6. Romero-Gomez, P., C. Y. Choi, Lansey, K. E., Preis, A., and Ostfeld, A. Sensor Network Design with Improved Water Quality Models at Cross Junctions. 10th Annual Water Distribution Systems Analysis Symposium, South Africa, August 20, 2008.

7. Weir, M. H. Microbial Dose Response Modeling in the 21st Century: The Development of Mechanistic Dose Response Models. Society for Risk Analysis (SRA) Annual Meeting, Boston, Massachusetts, December 2008.

8. Weir, M. H. and C. N. Haas. Effect of Host Species on the Dose Response of Inhaled *Bacillus anthracis* Spores. Society for Risk Analysis (SRA) Annual Meeting, Boston, Massachusetts, December 2008.

9. Weir, M. H. and C. N. Haas. Quantification of the Effect of Age on the Dose Response of *Variola major* (causative agent of smallpox) (Poster). Society for Risk Analysis Annual Meeting, San Antonio, Texas, December 2007.

10. Mitchell-Blackwood J., P. Gurian, and M. Weir. A Bayesian statistical modeling approach for *Bacillus anthracis* dose-response data. Society for Risk Analysis Annual Meeting, San Antonio, Texas, December 2007.
11. Durham, D. P. and E. A. Casman. Should We Worry About Plague in Urban Rats in the U.S. (*Best Student Paper in Ecology Award*). Society for Risk Analysis Annual Meeting, San Antonio, Texas, December 2007.
12. Weir, M. H. and C. N. Haas. Quantification of the Effect of Age on the Dose Response of *Variola major* (causative agent of smallpox) (Poster). Second Annual Department of Homeland Security University Network Summit on Research and Education, Washington DC, March 2008.
13. Tamrakar, S.B. and C. N. Haas. Dose-Response Model for *Burkholderia Pseudomallei* (Poster). Annual Department of Homeland Security University Network Summit on Research and Education, Washington DC, March 2008.
14. Huang, Y., T. A. Bartrand, and C. N. Haas. 2008. Incorporating Time Post Inoculation into a Dose Response Model of *Yersinia pestis* in Mice (Poster). Second Annual Department of Homeland Security University Network Summit on Research and Education, Washington DC, March 2008.
15. Haas, C. N., M. H. Weir, and T. A. Bartrand. Effect of Host Species on the Dose Response of Inhaled *Bacillus anthracis* Spores (Poster). Second Annual Department of Homeland Security University Network Summit on Research and Education, Washington DC, March 2008.
16. Hong, T., P. Gurian, N. Dudley Ward. Analytical Equations Relating Aerosol Risk to Surface Concentrations (Poster). Second Annual Department of Homeland Security University Network Summit on Research and Education, Washington DC, March 2008.
17. Herzog, A. Implications of Detection Limit of Various Methods for *Bacillus anthracis* in Computing Risk to Human Health. The Civil and Environmental Engineering Student Mini-Symposium, Michigan State University, April 2008.
18. Greenburg, D. Surrogate Selection Strategy: *Bacillus anthracis* as a Case Example for Fate and Transport Experiments (Poster). The Joint U.S. Environmental Protection Agency and Department of Homeland Security Conference on Real-World Applications and Solutions for Microbial Risk Assessment, Bethesda, Maryland, April 2008.
19. Eisenberg, J. Effects of Exposure Dynamics in Dose Response Relationships. The 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 2008.
20. Koopman, J. An Emerging Science of Environmental Infection Transmission Systems. The 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 2008.
21. Weir, M. H. Dose Response Modeling in the 21st Century: The Development of Mechanistic Dose Response Models (Poster). The 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 2008.
22. Weir, M. H. and C. N. Haas. Quantification of the Effect of Age on the Dose Response of *Variola major* (causative agent of smallpox) (Poster). The 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 2008.

23. Huang, Y., T. A. Bartrand, and C. N. Haas. Incorporating Time Post Inoculation into a Dose Response Model of *Yersinia pestis* in Mice (Poster). The 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 2008.

24. Tamrakar, S. B. and C. N. Haas. Dose-Response Model for *Burkholderia Pseudomallei* (Poster). The 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 2008.

25. Hong, T., P. Gurian, N. Dudley Ward. Analytical Equations Relating Aerosol Risk to Surface Concentrations (Poster). The 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 2008.

26. Mitchell-Blackwood, J., P. L. Gurian, and M. H. Weir. Bayesian Hierarchical Modeling to Estimate Interspecies Dose-Response Safety Factors (Poster). The Joint U.S. Environmental Protection Agency and Department of Homeland Security Conference on Real-World Applications and Solutions for Microbial Risk Assessment, Bethesda, Maryland, April 2008.

27. Durham, D. and E. Casman. Plague Dynamics in Urban Rodents. The 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 2008.

28. Casman, E. Risk Communication Planning for the Aftermath of a Plague Bioattack. The 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 2008.

29. Weber, R. O. and S. Gunawardena. 2008. The CAMRA Knowledge Management Approach (Poster). The 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 2008.

30. Gunawardena, S., C. MacDonald, and R. O. Weber 2008. Discovering Optimal Search Term Cardinality (Poster). The 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 2008.

31. Mitchell-Blackwood, J., P. L. Gurian, and M. H. Weir. A Hierarchical Model for Probabilistic Dose-Response Assessment of *Bacillus anthracis* (Poster). Second Annual Department of Homeland Security University Network Summit on Research and Education, Washington, DC, March 2008.

32. Weir, M. H. Dose Response Modeling in the 21st Century: The Development of Mechanistic Dose Response Models (Poster). Drexel University Tenth Annual Research, Innovation, Scholarship and Creativity Day 2008, Philadelphia, PA, April 2008.

33. Weir, M. H. and C. N. Haas. Quantification of the Effect of Age on the Dose Response of *Variola major* (causative agent of smallpox) (Poster). Drexel University Tenth Annual Research, Innovation, Scholarship and Creativity Day 2008, Philadelphia, PA, April 2008.

34. Huang, Y., T. A. Bartrand, and C. N. Haas. Incorporating Time Post Inoculation into a Dose Response Model of *Yersinia pestis* in Mice (Poster). Drexel University Tenth Annual Research, Innovation, Scholarship and Creativity Day 2008, Philadelphia, PA, April 2008.

35. O'Donnell, C., P.L. Gurian, D. Scarsella and R. Johnson. Threshold for Anthrax Vaccination (Poster). Drexel University Tenth Annual Research, Innovation, Scholarship and Creativity Day 2008, Philadelphia, PA, April 2008.

36. Madsen, J. and P. L. Gurian. A Valuation of the BioWatch Detection System (Poster). Drexel University Tenth Annual Research, Innovation, Scholarship and Creativity Day 2008, Philadelphia, PA, April 2008.

37. Mitchell-Blackwood, J. and P. L. Gurian. An Evaluation of the Risk Threshold for Prophylaxis and Treatment After An Anthrax Release (Poster). Drexel University Tenth Annual Research, Innovation, Scholarship and Creativity Day 2008, Philadelphia, PA, April 2008.

38. Hong, T., P. Gurian, and N. Dudley Ward. Analytical Equations Relating Aerosol Risk to Surface Concentrations (Poster). Drexel University Tenth Annual Research, Innovation, Scholarship and Creativity Day 2008, Philadelphia, PA, April 2008.

39. Mitchell-Blackwood, J., T. Hong, N. Dudley Ward, P. L. Gurian. Relating Human Health Risk to Environmental Concentrations of *B. anthracis* using Analytic Models. 11th Annual Force Health Protection Conference, Albuquerque, NM, 9 - 15 August, 2008.

40. Huang, Y., T. Hong, T. Bartrand, P. L. Gurian, C. N. Haas, R. Liu and S. Tamrakar. How Sensitive is Safe? Risk-based Targets for Ambient Monitoring of Pathogens (Poster). International Symposium on Spectral Sensing Research, Hoboken, NJ, June 2008.

41. Koopman, J. Using environmental transmission theory and data to parameterize contact networks. European Science Foundation Meeting on the Intersection of Models and Data, Utrecht, Netherlands, November 2008.

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43. Herzog, A., C. Rodriguez, K. Enger, M. Milbrath, O. Bucher, P. Okelo, S. Luster-Teasley, and Y. Huang. 2008. Risk Assessment: Release of Anthrax in an IRS Building. Group A Case Study: CAMRA 3rd QMRA Summer Institute, Michigan State University, East Lansing, MI.

44. Pandey, A., W. Betacourt, A. Baynton, A. Wright, K. Bush, S. Khan, K. Shaw, A. Coulliette. 2008. Adventure Vacations: Leaving Norovirus at the Dock. Group B Case Study: CAMRA 3rd QMRA Summer Institute, Michigan State University, East Lansing, MI.

45. Mendoza-Sanchez, I., F. Simmons, C. O'Donnell, M. Sato, A. Rajić, B. Mayer, A. Jenkins, J. B. Rose, and G. Medema. Tularemia in Water: A Quantitative Microbial Risk Assessment. Group C Case Study: CAMRA 3rd QMRA Summer Institute, Michigan State University, East Lansing, MI.

46. Gurian, P., I. Young, M. T. Pepe Razzolini, R. Johnson, B. Schmidt, C. Flemming, T. Hong, and A. Smith. Risk Assessment for H5N1 Influenza A: Border Inspection of Smuggled Goods Exposure. Group D Case Study: CAMRA 3rd QMRA Summer Institute, Michigan State University, East Lansing, MI.

(Briefings)
1. Haas, C. N., J. Rose, M. Nicas, P. Gurian, Y. Masago, R. Jones, T. A. Bartrand. Tuberculosis Risk Associated with Airline Travel. Briefing to Department of Homeland Security Chief Medical Officer. Washington, DC, 2007.

(Workshops)
1. Gurian, P. Statistical Analysis with the R Programming Language. Society for Risk Analysis Meeting, San Antonio, Texas, December 2007.

(CAMRA Workshops)
1-day QMRA Workshop, 108th American Society for Microbiology (ASM) General Meeting, Boston, MA, June 2008.
- Rose, JB: Risk Frameworks, Data Sets and Integration of Microbiological Fields
- Haas, CN: Dose-Response
- Sinclair, R: Exposure Assessment
- Gurian, P: Risk Characterization & Management

3rd QMRA Summer Institute, Michigan State University, East Lansing, MI, August 10-15, 2008.
- 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
- Haas, CN, Weir, M : Monte-Carlo Simulation
- 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 III (Sep 15 2007 to Sep 14 2008) for Project 1

1. Project 1, Project I
2. Investigators: Mark Nicas, Charles Gerba, Paul Keim, Syed Hashsham, Ryan Sinclair, Sonia Fankem, Alok Pandey, David Greenberg , David Wagner, Christopher Choi, Ian Pepper, Pedro Romero, Ryan Austin, Amanda Herzog, Jessica Henley, Rachael Jones
3. Project Goals (from proposal, additional 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 III (Sep 15 2007 to Sep 14 2008):
   Gerba Lab (UA):

   - Compete studies on inactivation of viral surrogates on various types of fomites and prepare manuscript
   - Conduct dispersion studies on coliphage MS-2 in dispersion in piped systems with Dr. Chris Choi
   - Select surrogates for survival of arenaviruses on fomites
   - Develop assay methods and viral stocks for arenaviruses survival studies
   - Assess risk model for fomites during norovirus outbreaks

   Choi Lab (UA):

   - Complete the water quality model (AZRED) based on the experimental data for mixing at junctions in laminar, transient, and turbulent regimes.
   - Run dispersion simulation scenarios using AZRED for quantitative microbial risk assessment (QMRA)
   - Develop prediction models using Artificial Neural Networks based on experimental data and modeling tools
   - Inject surrogates into water distribution systems at the Water Village and examine the prediction models

   Wagner Lab (NAU):

   - Validation of a potential surrogate for *Bacillus anthracis*
     - Several possible surrogates have been identified and, as the literature has major gaps of information related to our goals, we are continuing with experiments comparing the behavior of *Bacillus* species spores in varying environments (air, water, fomites, soil) and under various conditions (temperature, pH etc…) and over different time frames (a few hours using high temperatures versus a few years for lower temperatures). During year three, experiments will move into the BSL3 to compare the data already collected using non-virulent potential surrogate species to new data collected from fully virulent strains.

   - Determine real world parameters for fate and transport models
     - The fate and transport model parameters will be informed by the results of our comparative experiments. Values such as natural attenuation rates will be generated and be available for input to inform the models.

   - Validation of detection methods
     - We are continuing to develop an assay to detect the surrogate *Bacillus thuringiensis* and distinguish it from the other *Bacillus* species.

- Deliverables for year 3
  - SOP for comparative experiments using soil.
  - SOP for spore preparation, liquid comparisons, and fomite comparisons for the BSL3
  - Review paper of surrogate selection strategy for *Bacillus anthracis.*

Hashsham Lab (MSU):

- Environmental detection limit of *Bacillus anthracis* in water - literature review
- Environmental detection limit of *Bacillus anthracis* in air – literature review
- Environmental detection limit of *Bacillus anthracis* in soil – literature review
- Environmental detection limit of *Bacillus anthracis* on fomites-literature review
- Quantifying limits of risk estimates
- Experimentally evaluate detection limit for cultivatable method using P22
- Experimentally evaluate detection limit for cultivatable method using *Bacillus thuringiensis.*
- Modification of double layer agar method to distinguish between loss due to recovery or from loss due to decreased infectivity

Nicas Lab (UC Berkeley):

- (Markov chain model) – Develop a method for translating velocity vector and turbulent intensity values, as generated by computational fluid dynamics (CFD) modeling or by direct measurements, into transition probabilities for the Markov chain particle model. A central issue with the CFD translation is condensing information at 10,000 or more nondimensional room grid points into transition probabilities for far fewer cubic room air cells used in the Markov chain model. An issue common to both CFD predictions and direct measurements of room air velocities is mapping turbulence intensity (the random fluctuations in air velocities) to a turbulent eddy diffusion coefficient value as used in the Markov chain model. This segues to proposing a new project task (# 5 below).

- (Markov chain model) – Conduct aerosol release experiments. We have fabricated a test chamber in temporary space at the UC-Berkeley Richmond Field Station. The chamber is 10.5 ft long, 8 feet wide, and 8 feet high. The mean air velocity field (and its fluctuating components) will be measured with 3-dimensional anemometers. Fluoroscein-tagged particles with alternative aerodynamic diameters of 3 μm and 15 μm will be released in the chamber. The pattern of particle dispersion and settling will be measured by collecting, respectively, air samples and settling plate samples at different room locations. Fluorescein will be eluted from the sample media and fluorescein intensity quantified with a fluorometer.

- (Markov chain model) – Analyze the experimental aerosol release data. The experimental data on particle concentrations in air and deposition onto the floor at different room positions will be compared with predictions made by the Markov chain particle model given measured values for the mean room air velocities and turbulence. In addition, a colleague of Dr. Haas at Drexel University may be able to simulate particle dispersion and settling in the test chamber via CFD modeling. If that is the case, we will also compare the performance of the Markov chain and CFD methods, with the "gold standard" being the experimental data.

- (Markov chain model) – Draft a manuscript reporting the particle release data and the performance of the Markov chain model in predicting particle dispersion and settling.

- (New Goal: Turbulent Eddy Diffusion and Time-to-Mixing) – As mentioned under Task 1, a current question is how to map turbulence intensity, K (m min^{-1}), which reflects the random fluctuations in room air velocities, to a turbulent eddy diffusion coefficient value, D_T (m^2 min^{-1}). The latter parameter is used in the discrete-time Markov chain model and in more traditional continuous-time turbulent diffusion models. We propose to explore the relationship using the

time-to-mixing parameter, τ_{mix} (min). The latter is the time required for a neutrally buoyant tracer agent (for example, sulfur hexafluoride gas, carbon monoxide gas) released at the room center to disperse within the room such that the percent coefficient of variation of the tracer agent concentrations at different room positions is less than 10%. We propose to characterize the air velocity field (via 3-dimensional anemometry) in a sealed test room under different fan energy inputs, and measure the time-to-mixing τ_{mix} for these same conditions. The anemometry will provide an estimate of turbulence intensity K associated the same τ_{mix} value. A simple turbulent diffusion model of the room will provide a D_T value that corresponds to the observed τ_{mix} value. Thus, an empirical relationship between K and D_T can be established.

- (New Goal: Droplet Spray Exposure) – A major pathway for person-to-person infection with respiratory tract pathogens (for example, smallpox virus, SARS corona virus, pneumonic plague *Y. pestis*) 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. If the natural chloride content of saliva is insufficient for measurement in this system, sodium chloride 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

5. Research Activities
   Modeling dispersion
   Research activities entered by Christopher Choi

   Analyzing microbial dispersion data
   Evaluating detection limit
   Estimating risk characterization
   Identifying detection limit
   Research activities entered by Amanda Herzog

   Determining Inactivation
   Research activities entered by Alok Pandey

   Validating surrogates
   Measuring inactivation rates
   Creating method
   Comparing data
   Research activities entered by David Greenberg

   Modeling particle fate and transport
   Modeling dispersion
   Research activities entered by Mark Nicas

   Analyzing survival
   Comparing fate and transport
   Developing surrogates
   Research activities entered by Ryan Sinclair

6. Background and prior research (from learning units of the type Things I have read, those essential

references you want to include; from Year II, include summary of previous years):

7. Research Contributions this Year (how you advanced MRA, contributions and results from completed learning units; please list the numbers of the learning units, as follows:

Genetic characterization of highly touched and untouched fomites: LU (135)
Author(s): Amanda Herzog
When Analyzing microbial dispersion data we wanted to determine the genetic characteristics of influenza on touched and untouched fomites.
Experimental Design was 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. 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.

Survival of viral pathogens on fomites: LU (267)
Author(s): Ryan Sinclair
Analyzing survival: We wanted to find out the survival of various pathogens on fomites and evaluate the first-order die-off kinetics as an acceptable statistical model for survival by the three organisms studied in these investigations.
Experimental Design was as follows:
Summarize the research already completed into a publication

Particle fate and transport in a test chamber: LU (83)
Author(s): Mark Nicas
When Modeling particle fate and transport we wanted to predict the dispersion pattern of particles
Experimental Design was as follows:
release particle of known sizes into the air of a test chamber; measure the deposition pattern on the floor; measure the concentration pattern in air; compare the predicted measured values

Evaluation *B. thuringiensis* recovered from fomites-cultivation: LU (104)
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 was as follows:
This task involves an experimental evaluation of the detection limit of cultivatable method using Bacillus thuringiensis recovered from various fomites. Fomites of interest include plastic, laminar, and stainless steel with surface areas of 0.01 m2, 0.1 m2. Bacillus thuringiensis will be serial diluted in an application medium of water. A total of 50 μl of the sample will be applied to the fomite in a grid formation comprised of fifty 1 μL 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, 200 μL of TSB is distributed uniformly using a spreader (the surface and spreader are wiped). 1mL of the extraction solution will be used for cultivation.

MS-2 Phage and Salt Tracers to Characterize Axial Dispersion: LU (265)
Author(s): Ryan Sinclair
Comparing fate and transport: The transport and dispersion of microorganisms can be estimated through using salt tracers.
Experimental Design was as follows:
Inoculate bacteriophage MS2 into an experimental water distribution system. Characterize the

dispersion of it and salt tracers.

Criteria for Selection of Microbial Surrogates: LU (266)
Author(s): Ryan Sinclair
Developing surrogates: We wanted to find an all-encompassing criteria for selection of surrogates which is agreed by various professionals.
Experimental Design was as follows:
Review current literature, obtain ideas and knowledge from various professionals,

Validation of a surrogate for *B. anthracis*: fomites: LU (323)
Author(s): David Greenberg
When validating surrogates we wanted to find out if *B. thuringiensis* is a good surrogate for *B. anthracis*
Experimental Design was as follows:
Several potential surrogates selected from the literature search are placed on fomites including laminar, stainless steel, and polypropylene and over the course of two years CFU counts and DNA for qPCR are collected. D values are calculated to compare the survival of surrogates. CFUs and DNA data are compared for the compatibility of the two data sets

Validation of a surrogate for *B. anthracis*: liquid LT: LU (325)
Author(s): David Greenberg
When validating surrogates we wanted to find out if *B. thuringiensis* is a good surrogate for *B. anthracis*
Experimental Design was as follows:
Potential surrogates and *B. anthracis* are placed in ddH2O and CFU and DNA data is collected over two years

Inactivation of *B. anthracis* spores: LU (327)
Author(s): David Greenberg
When Measuring inactivation rates we wanted to find out Quantified *B. anthracis* inactivation rates.
Experimental Design was as follows:
B. anthracis spores are challenged for survival in short term liquid and soil experiments using different pH and temperature and in long term water and fomite experiments.

Validation of a surogate for *B. anthracis*: soil: LU (328)
Author(s): David Greenberg
When validating surrogates we wanted to find out if *B. thuringiensis* is a good surrogate for *B. anthracis*
Experimental Design was as follows:
Potential surrogates and *B. anthracis* Sterne are added to sterilized soil and CFU and DNA data is collected over two years for the long term experiments and over short time courses with changes in calcium and pH and temperature.

BSL 3 protocols for *B. anthracis* surrogate selection: LU (329)
Author(s): David Greenberg
When creating method we wanted to find out safety procedures for the experiments to compare selected surrogate against virulent *B. anthracis* strains
Experimental Design was as follows:
Create protocols for spore preparation and for comparative experiments to be conducted in the Bio Safety Level 3 facility.

Detecting spore survival with qPCR: LU (331)
Author(s): David Greenberg
When comparing data we wanted to find out if it is possible to use qPCR to see inactivation of bacterial spores
Experimental Design was as follows:

Collect DNA from all survival experiments and compare qPCR values of total DNA to CFU values

Validation of a surrogate for *B. anthracis*: liquid ST (74,79)
Author(s): David Greenberg
When validating surrogates we wanted to find out iIf *B. thuringiensis* is a good surrogate for *B. anthracis*
Experimental Design was as follows:
Comparing survival in liquid using different pH and heat challenges in short term experiments
Contribution:
Based on short-term attenuation in liquid, *B. thuringiensis* is a good surrogate for *B. anthracis*
Results:
Inactivation rates of *B. thuringiensis* are similar to *B. anthracis*

Evaluation P22 recovered from fomites using cultivation (102,116)
Author(s): Amanda Herzog
When evaluating detection limit we wanted to find the method and parameters which results in a high recovery at the detection limit (low concentration/large fomite surface area).
Experimental Design was as follows:
This task involves an experimental evaluation of the detection limit of cultivatable method using P22 recovered from various fomites. Fomites of interest include plastic, laminar, and stainless steel with surface areas of 0.01 m^2, 0.1 m^2. P22 will be serial diluted in application mediums of phosphate buffered saline tween-80 (PBST), tryptic soy broth (TSB) and water. A total of 50 µl of the sample will be applied to the fomite in a grid formation comprised of fifty 1 µL 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 (48cm^2), kimwipe (48cm^2) 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, 200 µL of TSB is distributed uniformly using a spreader (the surface and spreader are wiped). 1 mL of the extraction solution will be used for cultivation.
Contribution:
We showed the variability of P22 recovery as a function of surface type, humidity, application mediums, wetting agent, and the surface area.
Results:
Samples applied to the surfaces in TSB (78% at time zero) resulted in higher average recovery than in PBST (69%) or water (59%). Laminar (92%) had a higher average recovery at time zero than steel (70%) or plastic (45%). Size of the fomite affected the recovery of P22; for laminar at time zero the recovery decreased by 50% with the increase in surface size from 0.01 m2 to 0.1m2 using 1 wipe. At the initial time of application the average recovery was high (67%) but when the samples were dry the average recovery was low (0.91%). However, using a wetting agent and monitoring the relative humidity (30% or greater) resulted in an increase in recovery by 30% for dry samples.

Loss due to recovery Vs loss due to decreased infectivity of P22 (128,131)
Author(s): Alok Pandey
When determining inactivation we wanted to distinguish between loss due to recovery from loss due to decreased infectivity of P22 on fomites
Experimental Design was 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 3 ml bacto agar, 1ml TSB and 500 µL log phase-host cell culture with proper mixing and incubated in inverted position for 18-24 hr at 370 °C. Plaques were scored for the number of active P22 particles.
Contribution:
Low recovery in P22-fomite experiments is because of inactivation of the virus particles after drying

on the surface
Results:
There is no significant difference between the double agar layer method with recovery and the modified single agar layer method excluding the recovery after the P22 dried on the surfaces, although the exclusion of recovery showed slightly increased percentage of PFUs on plates.

Environmental detection limit for methods detecting *B. anthracis* (130,133)
Author(s): Amanda Herzog
When identifying detection limit we wanted to find out the environmental detection limit for the detection of Bacillus anthracis from the literature for each environmental matrix (water, air, soil, fomites).
Experimental Design was as follows:
Literature from published journal articles on the detection methods for the organism of interest was reviewed. Journal articles were collected using a number of key words on ISI Web of Science. References were then exported into an EndNote file. A manual screening was then conducted to eliminate any references that were not expected to contain relevant data. Data collected from the journals depended on the matrix (water, air, soil, and fomite) in which the research was conducted. For the environmental detection limit in water, data extracted from the journals in order to calculate the environmental detection limit of water were sampling volume, sample concentration, elusion/extraction volume, volume added to the reaction and total reaction volume. For the environmental detection limit in air, sampling volume, air flow rate, duration, sample concentration, elusion/extraction volume, volume added to the reaction, and total reaction volume. For the environmental detection limit in soil, sampling volume, sample concentration, elusion/extraction volume, volume added to the reaction and total reaction volume. For the environmental detection limit on fomites, surface area, surface seeding method, sample concentration, extraction volume, volume added to the reaction, and total reaction volume. In some cases recovery efficiency and extraction efficiency were available and noted.
Contribution:
We showed the current state of the detection methods for *Bacillus anthracis*.
Results:
Real-time PCR and PCR were the most sensitive methods for the detection of B. anthracis with a median instrument detection limit of 430 and 440 cells/mL, respectively. Raman spectroscopy and mass spectrometry were the least sensitive methods with the median instrument detection limit of $1.0x107$ and $8.0x107$ cells/mL, respectively. There were very few peer reviewed articles on the detection methods for B. anthracis in the environment. The most sensitive detection limits for the environmental samples were 0.1 spores/g for soil using PCR-ELISA, 17 spores/L for air using ELISA-biochip system, 1 spore/L for water using cultivation (sheep blood agar), and 12 CFU/cm2 for steel fomites using cultivation (sheep blood agar).

Relating time to mixing and air turbulence (139,140)
Author(s): Mark Nicas
Modeling dispersion: To develop a quantitative relationship between turbulence intensity and time to mixing
Experimental Design was as follows:
Measuring air velocities on 3 orthogonal axis at 2 chamber locations
Contribution:
There is a quantitative relationship between time to mixing and turbulence intensity
Results:
The results are available in Rachael Jones doctoral dissertation, 2008, UC Berkeley, attached to corresponding accomplishment unit 137

Quantifying risk estimates from IDL and EDL for *B. anthracis* (127,173)
Author(s): Amanda Herzog
When estimating risk characterization we wanted to find out the estimated risk from the instrument detection limit and the environmental detection limit.
Experimental Design was as follows:

Risk of mortality by inhalation of *Bacillus anthracis* spores will be estimated for concentrations corresponding to the environmental detection limit in air and the instrument detection limit. For each detection limit, a distribution of risks was calculated by the Monte Carlo method using 100,000 replicates in Crystal Ball® 7.3.1 (Oracle, 2007). The number of replicates was chosen so that the 90% confidence interval would not change over a range from one tenth to ten times the number of replicates used. Dose-response data for *B. anthracis* spores found that only the inhalation exposure route could be modeled by the exponential model. The probability that one organism will survive to initiate response, k, is generated from a pooled guinea pig and rhesus monkey data set. A distribution of 10,000 best fit k values generated using bootstrap replicates of that data set was provided by Dr. Timothy Bartrand of Drexel University and fit to a gamma distribution. Breathing rate was modeled as a Pareto distribution fit to the short-term breathing rates of adults (18 and up) of both sexes from rest to moderate activity (EPA, 1997). Exposure time was modeled as a uniform distribution from 1 minute to 8 hours. The range of PCR instrument detection limits were combined with the range of real-time PCR detection limits. Log transformed PCR and real-time PCR detection limits were checked for normality with a Lilliefors test and compared using ANOVA.

Contribution:
We showed the risk associated at the detection limits.
Results:
Testing dose-response functions for *B. anthracis* using the instrument detection limit and the environmental detection limit relates to estimates of risk limits of 0.520 or less.

Water Quality Modeling in Potable Water Distribution Systems (252,253)
Author(s): Christopher Choi
Modeling dispersion: The primary project goal is to develop and demonstrate a one-dimensional network water quality solver that properly accounts for incomplete mixing of solutes at pipe junctions and for axial dispersion of constituents along pipe links.
Experimental Design was as follows:
programming, experimental verification, benchmarking, code verification
Contribution:
Mixing at various junctions are not complete.
Results:
Experimental measurements described in paper on Accomplishment Unit #255 and #248

Loss due to recovery Vs loss due to decreased infectivity of P22 (116,128)
Author(s): Amanda Herzog
Once we learned:
We showed the variability of P22 recovery as a function of surface type, humidity, application mediums, wetting agent, and the surface area.
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 3 ml bacto agar, 1 ml TSB and 500 μL log phase-host cell culture with proper mixing and incubated in inverted position for 18-24 hr at 370 °C. Plaques were scored for the number of active P22 particles.

8. Outputs:
    1. Students Supported:
       Student Supported
       Ryan Austin was supported.
       Accomplishments by Christopher Choi

       Supported students

Amanda Herzog is being supported under the supervision of professor Syed Hashsham
Accomplishments by Amanda Herzog
Alok Pandey is being supported as Post Doctoral fellow under the supervision of Professor Syed Hashsham
Accomplishments by Alok Pandey

2. Students Graduated:
Graduation
Amanda Herzog completed her M.S. degree on December 5 2008, under supervision of professor Syed Hashsham from the dept. of Civil & Environmental Engineering at Michigan State University.
Accomplishments by Amanda Herzog

Rachael Jones Graduated
Rachael Jones Graduated, her doctoral dissertation, called "Experimental Evaluation of a Markov Model of Contamination Transport in Indoor Experiments with Application to Tuberculosis Transmission in Commercial Passenger Aircraft"2008, School of Public health, Division of Environmental Health Sciences, UC Berkeley She earned a PhD and now has a postdoctoral position at the University of Illinois
Accomplishments by Mark Nicas

Determining inactivation rates of viruses on indoor surfaces
Hendley., J.2008. Determining inactivation rates of viruses on indoor surfaces. University of Arizona, Tucson, Az. Masrer Thesis. The objective of this study were to develop a method to determine viral inactivation rates on fomites, to observe the inactivation poliovirus type 1, MS-2 and P22 on selected surfaces, and to determine how suitablr these viruses would be as surrogates. Overall, MS-2 appear to be the best surrogates as it give the least variable results and survived longer than the other viruses on fomites.
Accomplishments by Ryan Sinclair

3. Publications:
MIXING AT CROSS JUNCTIONS IN WATER DISTRIBUTION SYSTEMS: A NUMERICAL STUDY
Romero-Gomez, P., C. K. Ho, and C. Y. Choi, 2008, Mixing at Cross Junctions in Water Distribution Systems: Part I. A Numerical Study, ASCE Journal of Water Resources Planning and Management, 134:3, pp. 284-294. Abstract. The present study investigates solute mixing phenomena at various flow rates within a cross junction, which is commonly found in municipal drinking water distribution systems. Simulations using Computational Fluid Dynamics (CFD) are employed to model the solute concentrations leaving the junction when one inlet is comprised of clean water while the other inlet carries a solute at Re > 10,000. For a few exemplary cases, the resulting velocity vectors and contours of dimensionless concentration are presented to explain the detailed mixing mechanisms at the impinging interface. The turbulent Schmidt number (Sct), an important scaling parameter, is also evaluated. Experimental results were used to assess values of Sct for various flow conditions that accurately captured the detailed mixing processes within the junction. The present study clearly indicates that mixing at pipe cross junctions is far from "perfect". Incomplete mixing results from bifurcating inlet flows that reflect off one another with minimal contact time. Improving the existing water quality model based on accurate mixing data and simulations is important not only to predict concentrations of chemical species such as chlorine in water distribution systems, but also to prepare for potential intentional and accidental contamination events.
Accomplishments byChristopher Choi

MIXING AT CROSS JUNCTIONS IN WATER DISTRIBUTION SYSTEMS: AN EXPERIMENTAL STUDY
Austin, R. G., B. van Bloemen Waanders, S. McKenna and C. Y. Choi, 2008, Mixing at Cross Junctions in Water Distribution Systems: Part II. An Experimental Study, ASCE Journal of Water

Resources Planning and Management 134:3 pp. 295-302. Abstract. The present experimental study focuses on the characterization of complex mixing phenomena at pipe intersections within pressurized water distribution networks. To examine the complete mixing assumption at a cross junction, a series of experiments were conducted in the turbulent regime (Re > 10,000). The experimental setup consists of a cross junction with various sensors, pumps and a data acquisition system to accurately measure solute concentration. Selected experimental results are compared to computational fluid dynamics (CFD) results. In addition, the water quality model associated with a standard water distribution network simulator (EPANET) was re-evaluated based on CFD and experimental data. Corrections based on experimental results are incorporated into EPANET for use in a case study. The study concludes that the complete mixing assumption can potentially create considerable errors in water quality modeling. Furthermore, severe errors are likely to occur in systems with many cross type junctions due to bifurcation of the incoming flows.
Accomplishments byChristopher Choi

AXIAL DISPERSION IN A PRESSURIZED PIPE UNDER VARIOUS FLOW CONDITIONS
Romero-Gomez, P., Z. Li, C. Y. Choi, S.G. Buchberger, K.E. Lansey, and V.T. Tzatchkov, 2008, Axial Dispersion in Pressurized Pipe under Various Flow Conditions, 10th Annual Water Distribution Systems Analysis Symposium, South Africa. Abstract. Water quality models for municipal pipe networks commonly use the plug flow assumption to calculate axial mass transfer for all flow regimes. Classical works on axial dispersion, conducted five decades ago (Taylorï¿½??s theory), laid foundations that have been examined and applied to chemical and industrial processes for laminar and turbulent flows. However, these experimental findings have not been fully integrated into water quality models for pressurized water distribution systems. The plug flow assumption often leads to discrepancies when compared to experimental or field data in unsteady low flow (laminar and transitional) zones of municipal pipe networks. The present study examines the axial dispersion of a non-reactive tracer in a pipe under laminar and transitional flow conditions. Inlet concentration readings are used as upstream boundary conditions for Computational Fluid Dynamics (CFD) simulations and 1D Advection-Dispersion (AD) models. The resulting downstream concentrations are compared with analytical approximations to determine the reliability of each approach. The present work will improve our fundamental understanding of solute transport and enhance our ability to model and predict water quality in municipal distribution systems. Improved water quality models with accurate spatio-temporal axial dispersion patterns will be critical in optimizing water quality sensor placement, assessing models for early warning systems, and generating the exposure information needed for quantitative risk assessment.
Accomplishments byChristopher Choi

SENSOR NETWORK DESIGN WITH IMPROVED WATER QUALITY MODELS AT CROSS JUNCTIONS
Romero-Gomez, P., C. Y. Choi, Lansey, K. E., Preis, A., Ostfeld, A., 2008, Sensor Network Design with Improved Water Quality Models at Cross Junctions, 10th Annual Water Distribution Systems Analysis Symposium, South Africa. Abstract. Single- and multi-objective sensor network designs have relied on water quality models that assume instantaneous and complete mixing of species at junctions. However, recent findings show that the perfect mixing assumption at pipe junctions potentially results in erroneous outcomes in predicting water quality in pipe networks. The latest studies, through a series of computational and experimental approaches, provide a higher-accuracy water quality model. In the present study, sensor network designs in water distribution networks are reexamined using both the perfect mixing and non-perfect mixing assumptions. The optimization algorithm minimizes the number of sensors needed for detecting potential 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 two water quality models and resulted in two 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. Therefore, the improvement of water quality modeling will improve the effectiveness of early warning detection systems in the event of accidental or deliberate contamination.

Accomplishments byChristopher Choi

Development of a Comprehensive Solute Mixing Model (AZRED) for Double-Tee, Cross, and Wye Junctions
Choi, C. Y., J. Y. Shen, R. G. Austin, 2008, Development of a Comprehensive Solute Mixing Model (AZRED) for Double-Tee, Cross, and Wye Junctions, 10th Annual Water Distribution Systems Analysis Symposium, South Africa. Abstract. Municipal water distribution networks consist of numerous cross-, tee-, and wye- junction connectors. In recent years, 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 (AZRED v.1.0.0) was developed based on experimental results. The code was validated using a set of network-level experimental data. In the present study, 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. These findings are integrated into a water quality solver (AZRED v.1.1.0) suitable for large-scale network simulations. 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.
Accomplishments byChristopher Choi

Manuscript on the Instrument and Environmental Detection Limit
Manuscript to be submitted to a peer-reviewed journal. Title: Implications of Detection Limit of Various Methods for Bacillus anthracis in Computing Risk to Human Health.
Accomplishments by Amanda Herzog

Manuscript for Evaluation of P22 recovered from fomites
Manuscript on the evaluation of P22 recovered from fomites is in progress to be submitted to Applied Environmental Microbiology
Accomplishments by Amanda Herzog

Manuscript for modified method for loss due to decreased infectivity of P22 from fomites
Manuscript in Progress to be submitted to Applied Environmental Microbiology
Accomplishments by Alok Pandey

Paper on Estimating Risk of Tuberculosis Infection
Jones, RM, Y Masago, T Bartrand, C Haas, M Nicas and J Rose (2008): Characterizing the Risk from Mycobacterium tuberculosis in Commercial Passenger Aircraft using Quantitative Microbial Risk Assessment, Environ. Sci. Technol., in press
Accomplishments by Mark Nicas

Paper on results of relating time to mixing and turbulence intensity
Manuscript to be submitted to peer-reviewed journal with title, "Mixing of a point source contaminant within a room and estimation of turbulence parameters"
Accomplishments by Mark Nicas

Paper describing the results of the particle release experiment
Manuscript to be submitted to a peer-reviewed journal, "Experimental determination of the transport and fate of supermicrometer particles within a room under natural and forced mixing"
Accomplishments byMark Nicas

Persistence of Category A Select Agents in the Environment
This is a review entitled "Persistence of Select Agents Category A in the Environment" for publication in Applied Environmental Microbiology as a minireview. The research emphasizes the development of standardized testing methods for experiments assessing survival in aerosol, water, soil, and on fomites. In an intentional release, exposure may occur by routes in which the bioagent

is not transmitted in nature. The potential for transmission is a function of transport and persistence. Information on the environmental persistence is limited but essential for estimating where the greatest environmental exposure may occur. The purpose of this review is to assess the current information on the persistence of select agents on the CDC category A agent list in the environment and its implication in a terrorism response. Sinclair, R., Boone, S.A., Greenberg, D., Keim, P. and Gerba, C.P. (2007). Persistence of category a select agents in the environment. Appl Environ Microbiol. 74, 555-563.
Accomplishments by Ryan Sinclair

Pathogen surveillance through monitoring of sewer systems
This report assesses retardation of viruses and other select BACs in waste water streams. This report assesses the feasibility of monitoring sewage systems as an early warning system for the release of pathogens. This is especially useful for monitoring of intentional or accidental contamination events because most pathogens are released in urine, feces, or saliva during active infections. Under typical infection circumstances, these agents are therefore released to sewer systems in quantities that would be detectable with existing molecular and bio-sensing technology. The review presents conclusions on: (1) the potential biological agents that might be released into a sewage system; (2) the likely background level of those agents in sewage; (3) laboratory methods and detection; and (4) the probability of detecting select biological agents in sewage. Several nations currently have sewage surveillance systems, which can determine the occurrence of virulent poliovirus in communities to assess the need for vaccination. These public health surveillance programs have demonstrated greater sensitivity for detecting early stages of outbreaks than can be obtained through clinical disease detection in communities. The programs have been used to monitor the spread of poliovirus and in some cases have demonstrated that sewage monitoring can detect virulent poliovirus 10 to 90 days before the first case reporting of clinical paralysis. A field study in Finland demonstrated that viruses are greatly retarded in sewer systems allowing detection over many days after a one-time release event. These studies indicate that one infected person in 10,000 could be detected if at least 108 infectious viruses are released over a four-day period. Because 108 enteric viruses are excreted per gram of feces, it is very possible to monitor for pathogens of public health concern such as Smallpox, *Brucella abortus* and many others that would be normally released to sewage through urine or feces. Sinclair, R. G., C. Y. Choi, M. R. Riley, C. P. Gerba, 2009, Pathogen Surveillance through Monitoring of Sewer Systems, Advances in Applied Microbiology, Vol. 65
Accomplishments by Ryan Sinclair

4. Patents:
5. Presentations:
    CEE Student Mini-Symposium
    Presented at the Civil and Environmental Engineering Student Mini-Symposium on April 11 2008. Title: Implications of Detection Limit of Various Methods for *Bacillus anthracis* in Computing Risk to Human Health.
    Accomplishments byAmanda Herzog

    Surrogate selection strategy for *Bacillus anthracis*
    Poster presentation at the The Joint U.S. Environmental Protection Agency and Department of Homeland Security Conference on Real-World Applications and Solutions for Microbial Risk Assessment. Bethesda, Maryland
    Accomplishments by David Greenberg

6. Organization of workshops:

7. Participation in workshops:
    QMRA Summer Institute
    Completed the 3rd QMRA Summer Institute August 10-15 2008
    Accomplishments by Amanda Herzog
    QMRA Summer Institute

Completed the 3rd QMRA Summer Institute August 10-15 2008
Accomplishments by Alok Pandey

8. Case studies:
9. Algorithms developed:
10. Human Resource Development:
11. Funds Leveraged (additional funding. resources for free):

9. Outcomes (how your contributions can be used to better society):
Unit 79: Validated surrogate for for *B anthracis*
Unit 102: Risk assessors will have better knowledge about recovery and parameters that affect recovery
Unit 104: Risk assessors will have better knowledge about recovery and parameters that affect recovery
Unit 116: First responders responsible from recovering viruses from fomites will have better knowledge
Unit 127: Risk assessors will have better knowledge about risk at the detection limit.
Unit 128: PFUs scored from this method will show the number of active P22 particles as there is no loss due to recovery method involved.
Unit 130: Risk assessors will have better knowledge about evironmental detection limit
Unit 131: First responders responsible for recovering viruses from fomites will have better knowledge.
Unit 133: First responders responsible from detecting *Bacillus anthracis* will have better knowledge
Unit 140: It assists in estimating time to exposure in a room
Unit 173: First responders responsible from detecting *Bacillus anthracis* will have better knowledge of the risk.
Unit 252: Expected results will provide new methods to realistically predict and accurately simulate junction mixing and axial dispersion of soluble constituents transported throughout a typical municipal drinking water distribution system under laminar, transitional or turbulent flow conditions.
Unit 253: Accurate dose response results and corresponding risk assessment using the updated water quality model
Unit 265: Salt is a suitable surrogate tracer for microorganism experiments in straight pipes. The major limitation is that salt is incapable of estimating the tailing effect that occurs after a contamination event. The models developed through salt tracer studies can be incorporated to current water distributions system modeling software.
Unit 266: A document to guide researchers in the selection of microbial surrogates for experiments involving Biological Agents of concern.
Unit 323: Validating a surrogate (*B. thuringiensis*) for *B anthracis*
Unit 325: A validated surrogate for *B anthracis*
Unit 327: Parameters for fate and transport models
Unit 328: A validated surrogate for *B anthracis*
Unit 329: Protocols for the BSL 3
Unit 331: A fast and efficient method to collect data for spore survival experiments
Unit 135: Risk assessors and modelers will have better knowledge about genetic characteristics of influnzea
Unit 267: Development of a "cookbook" of inactivation coefficients for survival of viruses on fomites. A publication detailing the experimental results.

10. Integration with other projects (association between units in different projects): There were no research collaborations between members of Project Project I and other projects.
11. Tasks for Next Year: IV (Sep 15 2008 to Sep 14 2009)
12. Anticipated Technical Results and Developments (examples of potential learning units for next year, within possible also include potential outcomes):

CAMRA Report for Year III (Sep 15 2007 to Sep 14 2008) for Project 2

1. Project 2, Project II
2. Investigators: Joe Eisenberg, James Koopman, Ian Spicknall, Sheng Li, Nottasorn Plipat, Bryan Mayer
3. Project Goals (from proposal, additional 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 III (Sep 15 2007 to Sep 14 2008):
   Empirical
   1. Environmental contamination of dormitories with influenza viruses during influenza epidemics: Specimens are to be collected from a single dormitory once cases in that dormitory are identified from both common sites such as computer rooms and from dormitory rooms. QPCR is to be performed at Michigan State for influenza. This work will help define the potential for environmental samples to be used in analyzing influenza virus infection transmission systems and determining the potential effects of different interventions.
   2. Environmental mediation of Norovirus during outbreaks: Outbreaks identified by local health departments are to be investigated collaboratively with the health departments. We will take samples from general sites as indicated and will follow a protocol for sample collection in households with cases. This work will help define the potential for environmental samples to be used in analyzing norovirus infection transmission systems and determining the potential effects of different interventions.

   Theoretical

   1. Statistical models for analyzing randomized control trials of interventions to control infection transmission: The validity and precision of effect estimates for environmental control actions like wearing masks or disinfecting hands are to be further defined under conditions with realistically collectible amounts of data from individuals. Both direct individual effects and indirect population effect measurements are to be evaluated. Different statistical models involving dynamically linear multi-level assumptions and non-linear transmission system assumptions are to be explored. The non-linear models to be used include those specified in section "c" below. This work will help define the data and theory necessary to get an accurate picture of infection transmission system dynamics.
   2. Environmental Infection Transmission System (EITS) models are to be further elaborated and analyzed: The general model developed last year will be elaborated in several ways. The effects of stochastic processes given structural details will be defined. Detailed formulation specific to airborne and droplet-hand-fomite transmission will be developed and analyzed. This work will advance the conceptual framework for the science of environmental mediation of person to person transmitted infections.
   3. Statistical methods for analyzing longitudinal epidemic data and determining model aspects that could explain transmission mechanisms will be explored. The example will be longitudinal data from norovirus epidemics. Models with and without environmental compartments will be compared using likelihood filtering, least squares regression, and MCMC methods. This work will help choose appropriate statistical methods for assessing choices between transmission model formulations.
   4. Cumulative dose response models will be further elaborated and analyzed. The informative value of simple dosing patterns in cumulative dosing experiments will be explored. One focus will be on whether differing innate immune response dynamics could explain population level transmission dynamics for different pandemic or potential pandemic strains. This work will help define the contributions that could be made by cumulative dose response experiments to understanding the mechanisms and dynamics of pandemic influenza transmission.
   5. Models of human movement will be further elaborated and analyzed. Movement patterns that could alter the balance between aerosol and droplet-hand-fomite transmission will be further

explored. This work will establish a conceptual framework for designing observations on human contact patterns to make those observations more informative regarding modes of transmission.

6. The interaction of the phenomena addressed in "d" and "e" above will be explored by developing and analyzing models that incorporate both human movement and cumulative dose response in the same model. Direct integration of both model forms is not computationally feasible. This work will define computationally efficient ways of capturing of the joint effects of these two phenomena and help better assess whether this interaction could be a key factor in determining whether emergent flu strains become pandemic.

2. Research Activities
   Developing dynamic dose response models
   Modeling transmission
   Fitting data

3. Background and prior research (from learning units of the type Things I have read, those essential references you want to include; from Year III, include summary of previous years):

4. Research Contributions this Year (how you advanced MRA, contributions and results from completed learning units; please list the numbers of the learning units, as follows:

   The Effect of Exposure Dynamics in Dose Response Relationships (373,374)
   Author(s): Joe Eisenberg
   Developing dose response model: We are trying to find out the effect of differing temporal patterns of exposure on risk of infection
   Experimental Design was as follows:
   To help model infection transmission through the environment, we model within people the time between pathogen exposure and infection take off. Unlike previous dose-response models, our model does not assume that the risk of infection is the same whether pathogens are inoculated all at once or over one day. That would be true only if immunity can't kill pathogens before they start an infection. Our model captures how one pathogen affects the potential of immunity to keep subsequent particles from initiating an infection. Since the pattern of timing of airborne and surface spread pathogen arrivals differ, models like ours are needed to assess airborne versus surface spread infection risks. We show that previous approaches might overestimate infection transmission risk. But empirical data to fully fit our model is not currently available. Therefore, to accurately characterize risk, dose-response experiments will have to be conducted where doses are given across different times.
   Contribution:
   The relationships we model could markedly alter the risks generated by airborne versus fomite transmitted pathogens. They show that risk of infection based on single-exposure dosing trials cannot accurately inform transmission models that seek to predict risk or to assess the dominant route of transmission. Data are needed that measure the risk of infection as a function of both dose and time. Such data will help refine physiologically based dose-response models like the one presented here.
   Results:
   Characterizing infectivity as a function of pathogen dose is integral to microbial risk assessment. Dose-response experiments usually administer increasing infectious doses to subjects at one time. The models used to analyze experimental data assume time independence of doses. Real world exposure to pathogens, however, is a sequence of discrete inoculation events where immune effectors can keep inoculated pathogens from starting infections in manner dependent on dose timing. We model the dynamic processes generating dose-response probabilities by incorporating pathogen interactions with immune effectors that can kill pathogens in the period before infection becomes established. Model analysis reveals an inverse relation between the time over which exposure is accumulated and the risk of infection. Static dose-response models that assume time independence will thus overestimate risk. For instance, the empirical risk of infection for a dose of 313 pathogens Cryptosporidium parvum is 0.66. Our model predicts this same risk when inoculation occurs in a very short time of exposure, however, when the time of exposure is increased 100-fold the risk of infection is reduced to 0.09.

Anthrax Cumulative Dose Response Estimation Things that are in progress LU (336)
Author(s): Bryan Mayer
Fitting data: How does probability of infection (symptoms, or death) change when we analyze data that uses multiple dosing as opposed to a bolus dose?
Experimental Design was as follows:
A study was conducted in 1966 on inhalation anthrax using an observational animal study. Monkeys were placed in a wool sorting mill and received continuous exposure to aerosolized anthrax. We are using these data to fit our three parameter cumulative dose response model (manuscript in preparation; Pujols, Eisenberg, and Koopman) which incorporates pathogen growth and immune response in addition to the standard exponential model risk parameter.

5. Outputs:
    1. Students Supported:
       We are currently supporting 4 graduate students: Ian Spicknel, Sheng Li, Nottasorn Pilat, and Bryan Mayer
       Accomplishments by Joe Eisenberg
    2. Students Graduated:
    3. Publications:
       The Effect of Ongoing Exposure Dynamics in Dose Response Relationships
       This manuscript is in review in PLoS Computational Biology
       Accomplishments by Joe Eisenberg

       A Dynamic Dose-Response Model for Modeling Infection Transmission
       This manuscript is under review in Journal of the Royal Society Interface
       Accomplishments by Joe Eisenberg

       Dynamics and Control of Infections Transmitted from Person to Person Through the Environment
       Manuscript in review in American Journal of Epidemiology
       Accomplishments by Sheng Li

    4. Patents:
    5. Presentations:
       Using environmental transmission theory and data to parameterize contact networks
       This was a presentation in Utrecht, Netherlands to a special meeting funded by the European Science Foundation to discuss models that intersected with data in new ways and how these should be integrated into European modeling efforts. Date of presentation was Nov. 6, 2008
       Accomplishments by James Koopman

       Cumulative Dose Response Models for Environmental Transmission Analyses
       A poster presentation to the Epidemics conference
       Accomplishments by James Koopman

       Effects of Exposure Dynamics in Dose Response Relationships
       Presented at the Joint USEPA and DHS on Microbial Risk Assessment, April 9 2008
       Accomplishments by Joe Eisenberg

       An Emerging Science of Environmental Infection Transmission Systems
       Jim Koopman presented at the Joint USEPA and DHS on Microbial Risk Assessment April 9, 2008
       Accomplishments by Joe Eisenberg

    6. Organization of workshops:
    7. Participation in workshops:

8. Case studies algorithms developed:
9. Algorithms developed:
10. Human Resource Development:
11. Funds Leveraged (additional funding. resources for free):
6. Outcomes (how your contributions can be used to better society):
    Unit 373: A physiologically based dose response model
    Unit 374: We provide physiologically based dose response model that models how the immune process prevents infection
    :Unit 336: Influencing future animal studies to incorporate the idea of multiple inoculations. Observing the influence of temporal pattern of exposure on risk.
    Unit 372: We hope to provide a theoretical framework that incorporates environmental processes in transmission dynamics. This will provide a context to examine environmental interventions and inform collection of environmental specimens
7. Integration with other projects (association between units in different projects):
    Project III provided data sources for dynamic dose response model development.
8. Tasks for Next Year: III (Sep 15 2007 to Sep 14 2008)
9. Anticipated Technical Results and Developments (examples of potential learning units for next year, within possible also include potential outcomes):

CAMRA Report for Year III (Sep 15 2007 to Sep 14 2008) for Project 3

1. Project 3, Project III
2. Investigators: Chuck Haas, Carole Bolin, Mark Weir, Tim Bartrand, Sharon Nappier, Yin Huang, Toru Watanabe, Sushil Tamrakar
3. Project Goals (from proposal, additional goals):
    1. Comprehensive review of experimental dose response data available from open literature.
    2. Development and validation of dose response models for bioterrorism agents and other biological agents of concern.
    3. Experimental development of dose response data for infection and death related to oral challenge with *Francisella tularensis* in mice.
4. Tasks for Year III (Sep 15 2007 to Sep 14 2008):
    1. Start the process of validation as well as continue dose response modeling.
    2. Developing mechanistic dose response models.
    3. Dose-response Studies for multiple exposures for Tularemia
    4. Dr. Bolin is expected to continue with a *Francisella tularensis* animal study at Michigan State University (MSU). Once the dose response data from Dr. Bolin's lab is delivered to the dose response modelers for Project III, analysis of the incremental dosing strategy performed by Dr. Bolin's group will be performed and results prepared for publication.
5. Research Activities:

    Gathering dose response data.
    Determining dose response in mice.
    Developing dose response models.
    Fitting dose response models.

6. Background and prior research (from learning units of the type things I have read, essential references you want to include; from Year II, include summary of previous years):

    Equine Encephalitis – Literature Review: LU (218)
    Found equine encephalitis dosing experiments with mice, squirrels, monkeys, and guinea pigs
    (Berge, TO, Banks, IS, and Tigertt. 1961. Attenuation of Venezuelan equine encephalomyelitis virus by in

vitro cultivation in guinea-pig heart cells. Am J Hyg. 73:209-18.)

(Kuehne, RW, Sawyer, WD, and Gochenour, WS. 1962. Infection with aerosolized attenuated Venezuelan equine encephalomyelitis virus. Am J Hyg. 75:347-350.)

(Leung, MK, McLintock, and J. Iversen. 1978. Intranasal exposure of the Richardsons ground squirrel to western equine encephomyelitis virus. Can J Comp Med. 42:184-191.)

Things I have read units entered by Sharon Nappier

A Clinically Relevant model of SARS in mice: LU 297

Intranasal infection of A/J mice with MHV-1 produced pulmonary pathological features of SARS. From the fact that all MHV-1-infected A/J mice developed progressive interstitial pneumonitis, including dense macrophage infiltrates, giant cells and hyaline membranes, resulting in death of all animals, they concluded that A/J mice infected with MHV-1 would be a potentially useful small animal model of human SARS which defines its pathogenesis and suggests treatment strategies.

De Albuquerque, N., et al. Murine hepatitis virus strain 1 produces a clinically relevant model of severe acute respiratory syndrome in A/J mice. Journal of Virology, 2006; 80: 10382-10394.

Things I have read Learning Unit number 299

A transgenic mice expressing the human receptor for SARS coronavirus (SARS-CoV), which are very susceptible to SARS-CoV, have been used for an experiment of infection with recombinant SARS-CoV. DeDiego, ML, et al. Pathogenicity of severe acute respiratory coronavirus deletion mutants in hACE-2 transgenic mice. Virology, 2008; 376: 379-389.

Things I have read units entered by Toru Watanabe

7. Outputs:

Quantifying the Effect of Age on the Dose Response of Smallpox (184,187)

Author(s): Mark Weir

Modifying the dose response model: It is known clinically that smallpox affects the very young and the elderly more severely. Since the data for *Variola major* was age delineated it is hypothesized that age dependent dose response parameters can modify the dose response models to make age dependent dose response models for *Variola major*.

Experimental Design was as follows:

Take age delineated dose response data for *Variola major* (causative agent of smallpox) and determine if the exponential, beta Poisson and log probit dose response models can be modified to include an age dependency. Using current data reduction procedures to determine the best fitting dose response models, the inclusion of age dependent parameters will be approved or dismissed in order to modify the dose response models.

Contribution:

The current dose response models can be adapted for further refinement with modifications or additional parameters to take into account factors other than dose. This can be expanded to include microbial growth kinetics, time since initial inoculation of the host or other mechanistic factors.

Results:

The modified exponential and beta Poisson dose response models showed an improvement in the ability to predict the observed risk of death from *Variola major* (smallpox causative agent). The modification is in the form of an exponential regression model for k and N50 parameters in the exponential and beta Poisson models respectively, and a linear regression model for alpha in the beta Poisson model. Overall the beta Poisson model showed a 72% increase in the ability to predict the risk of death from smallpox. This is the first inclusion of age dependency into a dose response model for microbial risk assessment.

Oral Dose Response for *Francisella tularensis* in mice--Trial 1 (120,215)

Author(s): Carole Bolin

When determining dose response we hypothesize that true oral exposure to fluids containing *F. tularensis* will have different dose response parameters than intra-gastric inoculation and that this route of inoculation will more accurately mimic exposure that occurs during water borne outbreaks of tularemia.

Experimental Design was as follows:

C57BL6 mice will be exposed to different doses of three different strains of *F. tularensis ssp tularensis* to determine if there are strain differences in virulence in this model of infection and also to provide a broad estimate of the dose response curve for oral exposure. Oral inoculation will be used and this will mimic natural exposure to *F. tularensis* in water. Mice will be exposed and monitored for the development of clinical signs of disease. Groups of mice will be euthanized at 1, 2, 3, 4, and 14 days post exposure and liver, lung, spleen, and lymph nodes will be assessed for pathologic lesions and for bacterial burden.

Contribution:

The model of oral inoculation was successful in reproducing disease and provided a coarse estimate of the oral dose response parameters for tularemia in mice.

Results:

All three strains of *F. tularensis* were virulent in mice when administered orally. The dose response parameters for the various strains were determined and strain MA00-2987 was selected for further study. The dose response results were used to design the second trial to better define the low end of the oral dose response. The pathogenesis of tularemia induced by oral inoculation appears to be different than that produced by intra-gastric inoculation in that lung infection occurs sooner during the course of disease after oral exposure. This is consistent with our stated hypothesis.

Oral Dose Response for *Francisella tularensis* in Mice--Trial 2 (126,216)

Author(s): Carole Bolin

Determining dose response: We hypothesize that true oral exposure to fluids containing *F. tularensis* will have different dose response parameters than intra-gastric inoculation and that this route of inoculation will more accurately mimic exposure that occurs during water borne outbreaks of tularemia

Experimental Design was as follows:

C57BL6 mice will be exposed to dilutions of the Massachusetts strain of *F. tularensis* by oral inoculation. The dose range chosen was from 10(5) to 10(1) CFU based on the results of the first trial in this experiment. This second study was done to provide additional data at the low end of the dose response curve for this agent and route of inoculation. Clinical signs and quantitative bacterial counts were determined in groups of mice that were euthanized 1, 2, 3, 4, or 5 days post exposure.

Contribution:

A model of oral dose response to *F. tularensis* has been validated with additional data at the low dose range strengthening the dose-response curve.

Results:

Dose response parameters at the low end of the dose response curve were strengthened. The data from this study was pooled with data from the first trial. Statistical analysis is underway to determine the dose response model with best fits the data and to analyze the dose-response parameters to 2 different outcomes: 1) infection; and 2) disease (i.e. clinical signs).

How does host species effect the dose response of anthrax (279,283)

Author(s): Mark Weir

Fitting dose response model: Much work has been performed to attempt to describe the dose response relationship for inhalation of *B. anthracis* spores. There have been numerous animal models each of which describe the dose response relationship for that animal. The goal is to determine if these animal models can be pooled together, which then states that the dose response relationships are derived form the same distribution therefore they have similar responses and can be described with one overall dose response model.

Experimental Design was as follows:

Take the current dose response data mined from the open literature, fit dose response models to these animal models independently to determine the dose response relationship for each animal model. Then group the animal models into one large data set and attempt to fit an overall dose response model to the pooled animal model data. If the fit of the pooled dose response model is acceptable, then the animal models come from the same distribution and can be described with an overall dose response model.

Contribution:

Two very different animal models (guinea pig and rhesus monkey) could be pooled thereby giving an

overall model for drastically different host species. This gives credence to the idea of extrapolating these models to humans without any or much need of an inter-species extrapolation factor. Also, the dose response models when aerosol diameter is included confirm that aerosol diameter of the spore does affect the risk of death to the host. The LD50 decreased with decrease in aerosol diameter. Other CDC bioterror category agents (*Yersinia pestis, Francisella tularensis and Brucella suis*) displayed the same or similar trends with aerosol diameter.

Results:

It was found that only guinea pigs exposed to varied diameter size aerosol of *B. anthracis* ATCC-6605 strain could be pooled with rhesus monkeys exposed to the vollum strain. The other two guinea pig animal models, one with small diameter aerosol (~1 um) of the vollum strain and guinea pigs exposed to the vollum strain with undefined aerosol size could not be pooled with any other group. The effect of aerosol size was also determined to alter the LD50 for the animal groups, which had the aerosol size defined and examined in the study. Smaller aerosol sizes allowed for lower LD50 values for both guinea pigs and rhesus monkeys, which corresponds to prior knowledge of aerosol diameter of *B. anthracis*.

Time-dose-response model (296,298)

Author(s): Yin Huang

When fitting dose response model we wanted to find out if time-dose-response model can provide significantly acceptable fit to the survival dose response data

Experimental Design was as follows:

Searching open literature for survival dose response data, fitting time-dose-response model to the data, evaluating the fit

Contribution:

These new models can thus describe the development of animal infectious response over time and represent observed responses fairly accurately.

Results:

Time-dose-response model provided significantly acceptable fits to the animal survival data.

Dose-response model for SARS coronavirus (288,302)

Author(s): Toru Watanabe

When modeling dose response model we wanted to find out 1) Dose-response model for SARS coronavirus. 2) Infectivity of SARS coronavirus.

Experimental Design was as follows:

1) Collecting datasets for infection of animals with SARS coronavirus. 2) Fitting the dose-response models to the datasets.

Contribution:

The model developed here is the sole dose-response model for SARS-CoV at the present.

Results:

1) The pooled datasets were fit to beta-Poisson and exponential models with the maximum likelihood method. The exponential model (k = 410) could describe the dose-response relationship of the pooled datasets. The beta-Poisson model did not provide a statistically significant improvement in fit. 2) The 10 and 50% infectious doses of SARS-CoV were estimated at 43 and 280 PFU, respectively. Its estimated infectivity was comparable to that of HCoV-229E, another coronavirus known as an agent of human common cold, and also similar to those of some animal coronaviruses belonging to the same genetic group. 3) Moreover, the estimated dose of SARS-CoV for apartment residents during the outbreak was back calculated from the reported number of cases. The developed model resulted in an estimated dose to apartment residents of SARS-CoV between 16 and 160 PFU/person, depending on the floor.

Risk-Based Targets for Ambient Monitoring of Pathogens (300,306)

Author(s): Yin Huang

When determining risk threshold we wanted to find out if there is a critical environmental sampling rate of a PCR sensor associated with a threshold risk to determine whether or not the immediate post-exposure prophylaxis option should be taken

Experimental Design was as follows:
Designing a decision tree to calculating the risk threshold based on the cost-benefit analysis, determining the corresponding dose of pathogen to the particular risk, determining the environmental sampling rate for the PCR sensor
Contribution:
It shows how decision analytic approach and quantitative dose-response models may be used to inform environmental sampling rates.
Results:
Based on the risk level of concern for *Y. Pestis* of 1.5(10-4) the sensor's sampler should take in 92.4 liter, air per minute to detect the average environmental concentration corresponding to this risk level.

Dose-Response Model for Lassa Virus (304,316)
Author(s): Sushil Tamrakar
Developing dose response: we wanted to estimate risk from Lassa virus on the basis of a dose-response model
Experimental Design was as follows:
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:
Given this estimate, and the duration of exposure and inhalation rate, an air concentration corresponding to this risk can be computed.
Results:
1-Inbred guinea pigs are significantly more sensitive to subcutaneous exposure to Lassa virus than their out-bred counterparts. 2-Out-bred animals administered Lassa virus by aerosol showed a Beta-Poisson response, indicative of heterogeneity as well. 3-A level of risk of 1/10,000 would correspond to an exposure of 0.003 organisms.

Dose-Response Model for *Burkholdria pseudomallei* (Melioidosis) (310,319)
Author(s): Sushil Tamrakar
Developing dose response model: a Dose-Response Model for the bacteria *Burkholderia pseudomallei*
Experimental Design was as follows:
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:
The doses which result in a risk of 1/1000; the corresponding doses for BALB/c mice, C57BL/6 mice and diabetic rat are 0.1, 10 and 1.0 organisms respectively. In other words, BALB/c mice need 10 times less doses of *B. pseudomallei* (intranasal exposure) than diabetic rats (exposed intraperitoneally) and C57BL/6 mice need 10 times more doses (intranasal exposure) to have risk of 1/1000. Actual exposure in the environment will be very low dose and hence the model will certainly be benifited for the decision makers to assess risk.
Results:
1-Both the strains of mice (C57 BL/6 and BALB/c)showed similar responses in term of dose-response model as both of them resulted in Exponential dose response. 2-In intraperitoneally inoculated Guinea pigs, the response was best fit by the Beta-Poisson distribution. In contrast to above models, the diabetic rats inoculated with *B. pseudomallei* intraperitoneal route showed both Log-probit and Beta-Poisson responses. 3-Diabetic rats are more susceptible to *B .pseudomallei* than C57BL/6 mice at lower doses less than 10000 CFU. At 10x4 CFU, the responses were almost same (0.63 and 0.65), where as at 1 CFU, the response in diabetic rats were 15 times that of C57BL/c mice. Similarly at 100 CFU, responses in diabetic rats were 11 times higher than that of mice.

Dose-Response Model for Coxiella burnetii (Q fever) (311,321)
Author(s): Sushil Tamrakar
Developing dose response model: we wanted to develop a dose-response model for Q fever
Experimental Design was as follows:
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:
The Q fever is highly infective disease caused by Coxiella burnetii. An average of 6.6 organisms are sufficient to infect 50% of exposed population (human).
Results:
1-The best fit model for the severe combined immunodeficient (SCID) mice exposed intraperitoneally to C.burnetii was the Beta-Poisson. 2-C57BL/6J mice exposed intraperitoneally to C. burnetii were more resistant to infection than C57BL/10ScN mice. The LD50 for the C57BL/6J was 1.22×10^{10} and that of C57BL/10ScN was 1.76×10^{8}. 3-The best fit model for aerosol exposure of humans is the Beta-Poisson. 4-A single bacterium is estimated to cause infection to 19% of the exposed population.

Dose-response model for influenza A virus Things that are in progress LU (294)
Author(s): Toru Watanabe
Modeling dose response: 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 was as follows:
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.

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

8. Outputs:
   1. Students Supported: Yin Huang, Sushil Tamrakat
   2. Students Graduated: Timothy A. Bartrand
   3. Publications:
      Weir M.H., Haas C.N. (under review) Quantification of the Effect of Age on the Dose Response of *Variola Major*, Human and Ecological Risk Assessment. This publication will mark the first inclusion of age dependent dose response parameters for the exponential and beta Poisson models in microbial risk assessment.
      Accomplishments by Mark Weir

      Bartrand T.A., Weir M.H., Haas C.N.(2008) Does Response Models for Inhalation of *Bacillus anthracis* Spores: Interspecies Comparisons. Risk Analysis 28(4) pp. 1115-1124 This work detailed the efforts in pooling across host species as well as quantifying the effect of aerosol diameter on the dose response of inhaled anthrax spores.
      Accomplishments by Mark Weir

      The article has been published in "Journal of Human and Ecological Risk Assessment". Tamrakar, SB and Haas, CN. 2008. Dose-Response Model for Lassa Virus. Human and Ecological Risk Assessment. 14(4): 742-752.
      Accomplishments by Sushil Tamrakar

      The article has been published in "Journal of Applied Microbilogy" Tamrakar, SB and Haas, CN. 2008. Dose-Response Model for Burkholderia pseudomallei (melioidosis). Journal of Applied Microbiology. 105(5):1361
      Accomplishments by Sushil Tamrakar

      Huang Y., Bartrand, T.A., and Haas, C.N. (Under Review) Incorporating time post inoculation into a dose response model of *Yersinia pestis* in mice. Journal of Applied Microbiology.

Accomplishments by Yin Huang

Huang Y., and Haas, C.N. (Under Review) Time-to-dose response models for microbial risk assessment. Risk Analaysis
Accomplishments by Yin Huang

Huang Y., Bartrand, T.B., Gurian, P.L., Haas, C.N., Liu, R., and Tamrakar S.B. (Under Review) How sensitive is safe? Risk-based targets for ambient monitoring of pathogens. IEEE Sensors Journal.
Accomplishments by Yin Huang

4. Patents:
5. Presentations:
The work completed in learning unit 187 was presented to the Society of Risk Analysis Annual Meeting in San Antonio, TX. Weir, MH and Haas, CN. Quantification of the Effects of Age on the Dose Response of *Variola major* in Suckling Mice (poster). Society for Risk Analysis (SRA) Annual Meeting, Baltimore, Maryland December 3-6, 2006.
Accomplishments by Mark Weir

The work completed in learning unit 187 was presented to the 2007 Annual Department of Homeland Security University Network Summit, in Washington DC.   Weir, MH and Haas CN. Quantification of the Effects of Age on the Dose Response of *Variola major* in Suckling Mice (poster).
Accomplishments by Mark Weir

The work completed in learning unit 187 was presented to the Joint Environmental Protection Agency and Department of Homeland Security Meeting on Microbial Risk Assessment and Bioterrorism. Weir, MH and Haas CN. Quantification of the Effects of Age on the Dose Response of *Variola major* in Suckling Mice (poster).
Accomplishments by Mark Weir

The work being performed in developing mechanistic dose response models was presented to the Joint Environmental Protection Agency and Department of Homeland Security Meeting on Microbial Risk Assessment and Bioterrorism. Weir MH Bartrand TA and Haas CN. Dose Response in the 21st Century: The Development of Mechanistic Dose Response Models (poster).

The work completed in learning unit 187 was presented to the Drexel University Annual Research Day, in Philadelphia, PA, May 2008. .   Weir, MH and Haas CN. Quantification of the Effects of Age on the Dose Response of *Variola major* in Suckling Mice (poster)
Accomplishments by Mark Weir

Huang, Y., Hong, T., Bartrand, T.B., Gurian P.L., Haas, C.N., and Tamrakar, S.B. (2008) How sensitive is safe? Risk-based targets for ambient monitoring (poster).
This poster was presented to the International Symposium on Spectral Sensing Research, Hoboken, NJ, June 23-28, 2008.
Accomplishments byYin Huang

Huang, Y., Bartrand, T.B., and Haas, C.N. (2008) Incorporating time post inoculation into a dose response model of *Yersinia pestis* in mice (poster)
This poster was presented at: (1)Department of Homeland Security University Network Summit on Research and Education, Washington DC, March18-20, 2008, (2)The 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, and (3)Drexel University Research Day, Drexel University, Philadelphia, PA, 2008.
Accomplishments byYin Huang

6. Organization of workshops:
7. Participation in workshops:
8. Case studies algorithms developed:
9. Algorithms developed:
10. Human Resource Development:
11. Funds Leveraged (additional funding. resources for free):
12. Other:
    Two sets of mouse experiments were completed and the model of oral exposure *to F. tularensis* was validated. Data analysis continues but preliminary analysis has yielded a dose response curve for oral exposure with two outcomes: 1) infection, and 2) disease. Data is being used to inform the models used in other projects.
    Accomplishments by Carole Bolin

9. Outcomes (how your contributions can be used to better society):
Unit 120: Better guidelines for environmental clean up of water contaminated by *F. tularensis.*

Unit 126: Better guidelines for environmental clean up of water contaminated by *F. tularensis* and improved dose-response models for this disease and exposure route.

Unit 184: Modified dose response models that take into account the age of the host to assess the risk specific to the host's age group. Publication detailing the development and relevance of the modified dose response models to the youngest populations.

Unit 187: Modified versions of the exponential and beta Poisson dose response models that take into account the age of the host within the parameters for these models. An adaptation of the original maximum likelihood estimation (MLE) code used in dose response model fitting to fit the modified dose response models. And a publication currently under review by Human and Ecological Risk Assessment describing this work and results.

Unit 211: An overall model that informs the effective dose of *B. anthracis* and *N. meningitidis* which can easily be expanded to other pathogens where growth data is available and the pathogenesis is well defined. A stochastic MatLab model that determines effective dose for respiratory pathogens. Once it is shown that this type of model is feasible for the respiratory tract, other exposure routes such as ingestion can be developed using the same basic framework. Increased accuracy and a decrease in uncertainty on clean up goals and protection of first responders and medical professionals, as well as true detection limits for sensor and alert systems.

Unit 215: A model of oral dose response to *F. tularensis* has been validated.

Unit 216: A valid dose-response curve for oral exposure to *F. tularensis* in mice.

Unit 218: Collected papers for dose response modeling

Unit 283: An overall dose response model which describes the dose response relationship for two very different host species. And a quantification in the change of the dose response with change in the diameter of the aerosol being used.

Unit 288: The model will enable us to evaluate the risk of infection with SARS coronavirus.

Unit 296: Time-dose-response model could describe and predict the animals survival fairly accurately.

Unit 297: The dataset obtained in their experiment was employed for our development of dose-response model for SARS coronavirus.

Unit 298: The outcome may be used for the improved understanding of pathology or as a component of an epidemiological investigation.

Unit 299: The dataset was employed for our development of dose-response model for SARS-CoV
.

Unit 300: It could provide a framework for optimizing sensing systems.

Unit 302: The model developed would enable us to understand the possibility for reemergence of SARS in the future.

Unit 304: Dose-response model for Lassa virus

Unit 306: This analysis is intended primarily to outline a framework for how sensor systems may be informed by risk assessment.

Unit 310: Estimation of risk among the exposed population

Unit 316: Inbred population is more susceptible to *Burkholderia pseudomallei* than outbred population indicating the heterogeneous nature of infection. The log Probit model predicts the risk lower than the Beta-Poisson does.

Unit 319: Dose-Response Model for Melioidosis and supporting the outbreak data regarding the susceptibility in diabetic population.

Unit 321: Dose-Response Model for Q fever in human volunteers.

10. Integration with other projects (association between units in different projects): There were no research collaborations between members of Project Project III and other projects.
11. Tasks for Next Year: IV (Sep 15 2008 to Sep 14 2009)
12. Anticipated Technical Results and Developments (examples of potential learning units for next year, within possible also include potential outcomes):

CAMRA Report for Year III (Sep 15 2007 to Sep 14 2008) for Project 4

1. Project 4, Project IV Drexel
2. Investigators: Patrick Gurian, Jade Blackwood, Tao Hong
3. Project Goals (from proposal, additional 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 III (Sep 15 2007 to Sep 14 2008):

1. Interpreting environmental sampling for *B. anthracis*
An integrated model of *B. anthracis* dispersion in an indoor environment and dose-response has been developed to estimate risk following a release. Progress in this area is described below.

   a. Linking of Surface Concentrations to Risk: Equations, charts, and tables have been developed relating environmental concentrations to risk. This correspondence between risk and sampling results offers a means to interpret the results of surface sampling and guide remediation decisions.

b.   Sampling Guidelines: The results of the integrated model have been applied to estimate required sampling areas for surface samples and volumes and flow rates for air samples.

c.   Model Sensitivity Analysis: A sensitivity analysis on the *B. anthracis* release model has been conducted to identify key uncertainties. The level of risk at which a response action is justified has been identified as a key uncertainty and further efforts to address this uncertainty are being undertaken.

d.   Verification Against Previous Modeling: A comparison between the model used here and that of Sextro et al. (2002) has established that our model is consistent with previous knowledge of *B. anthracis* fate and transport.

2.   Hierarchical Modeling of Dose-Response Variability

This task is investigating how host species and strain variability may be modeled by using Bayesian hierarchical methods. This approach views dose-response model parameters for a particular species as deriving from a hyper-distribution describing variability between host species/pathogen strains. Thus estimates of uncertainty will be driven not only by the amount of data but by the observed interspecies/interstrain variability (the variance of the hyper-distribution). Past progress included the identification of suitable data for dose-response models for *B. anthracis* by Project III. In this year we fit the model to the anthrax data, consulted further with Project 3 to identify potential tularemia data sets which might be appropriate for the hierarchical dose-response modeling, and fit a model to a new data set provided by the U.S. Army's Center for Health Promotion and Preventative Medicine.

3.   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 is assessing the level of risk at which remediation and medical treatment become justified based on conventional cost-effectiveness benchmarks for risk reduction. This involves the following tasks:

a.   Identification of Model Inputs: The input parameters identified in the literature review, the equations governing the model, and key results are being compiled.

b.   Development of Decision Tree Framework to Identify Threshold Risk Levels: A decision tree framework is being developed to model the decision to response to a risk or take no action. A sensitivity analysis can then be performed to identify the risk level at which response actions are justified by benefit-cost analysis.

5.   Research Activities

Research activities have included 1) verifying the results of the *B. anthracis* fate and transport model with the model of Sextro et al. (2002) 2) fitting Bayesian hierarchical models and developing predictive dose-response relationships, 3) identifying sampling requirements for surface and aerosol sampling based on dose-response functions recently developed by Project III, and 4) assessing risk levels at which response measures are justified based on benefit-cost considerations.

6.   Background and prior research (from learning units of the type Things I have read, those essential references you want to include; from Year II, include summary of previous years):

Project III has provided dose-response functions needed for us to develop links between environmental concentrations and risk. In addition, Project III has identified suitable data sets for Bayesian hierarchical dose-response modeling. Key inputs from outside of CAMRA include the *B. anthracis* fate and transport model of Sextro et al. (2002) and the *B. anthracis* decision model of Fowler et al. (2005).

7.   Outputs:

1. Students Supported:

   Tao Hong, doctoral student

   Jade Mitchell-Blackwood, doctoral student

   April Wright, MPH student

   John Madsen, MPH student

2. Students Graduated: None

3. Publications:

   Under Review:

Yin Huang, Tao Hong, Timothy Bartrand, Patrick L. Gurian, Charles N. Haas, Ran Liu and Sushil Tamrakar "How Sensitive is Safe? Risk-based Targets for Ambient Monitoring of Pathogens," submitted to the *IEEE Sensors Journal.*

   Abstract:

   Biological agents present hazards at concentrations far below those of concern for most chemical agents. Detecting such low concentrations poses a great challenge to environmental monitoring systems. This study proposed a framework to address the questions of 1) what level of risk would trigger the use of countermeasures, 2) what environmental sampling rates would be needed to detect the target risk level. In the first part of the framework, a decision model is developed to assess the costs and benefits of prophylactic antibiotic treatment for *Yersinia pestis* (*Y. pestis*) as a function of the risk of illness. A sensitivity analysis is then conducted to identify a threshold level of risk at which medical treatment of exposed individuals is justified. Risk levels of 1.5×10^{-4} are estimated to be sufficient to justify treatment. A dose-response function is developed to map these risk levels to delivered doses to individuals. Estimates are that an average dose of 1.8 organisms is sufficient to trigger medical treatment for an exposed population. A range of human breathing rates are used to estimate the environmental sampling rates required to detect air phase concentrations corresponding to this dose over an 8-hour exposure period. The environmental sampling rates for *Lassa virus* are two orders of magnitude greater than for *Y. pestis*, while those for *Bacillus anthracis* (*B. anthracis*) are an order of magnitude lower. These sampling rates represent idealized goals for the sensitivity of detector systems. By linking environmental sampling rates to risk-based goals for detection, this paper provides a framework for optimizing sensing systems.

   Patents: None

   4. Presentations:

1. Mitchell-Blackwood J., P. Gurian, M. Weir. "A Bayesian statistical modeling approach for *Bacillus anthracis* dose-response data," Society for Risk Analysis Meeting, San Antonio, Texas, December 2007.

   Abstract:

   Project Scope: To assess the susceptibility of unobserved species on the basis of species with observed susceptibilities, a Bayesian meta-analysis is used to analyze experimental data from three different studies. The data obtained from the studies provided four sets of host-species/organism-strain groups

for analysis as combined data using a hierarchical model. Parameters describing the susceptibility of individual species are modeled as deriving from a distribution describing the variation of susceptibilities among different species. Hyperparameters defined the prior distribution of the dose-response parameters for the population of host species and strains. Markov Chain Monte Carlo (MCMC) methods were used to develop posterior distributions of exponential dose response model parameters for each species. A sensitivity analysis on the prior distribution was conducted to evaluate its effect on the resulting posterior distributions. This is an important factor to evaluate when the sample size is small as is typical with dose-response studies. Recent Progress: A Bayesian hierarchical statistical approach to fitting dose response parameters for Bacillus anthracis was compared to a classical, or frequentist, likelihood-based approach. The Bayesian approach uses a fully probabilistic framework to characterize parameter uncertainty. Confidence intervals for human dose-response from the Bayesian hierarchical model were much larger than for a classical approach, but the classical pooling process requires a much stronger assumption about the relatedness of humans and other species. Future Plans: A major challenge is to properly represent the degree of relatedness of different dose-response experiments. A framework for future research in this area is to consider two attributes for each experiment, microbial strain virulence and host species susceptibility. An autocorrelation function based on degree of difference on these attributes can then be used to represent the relatedness of different dose-response experiment in a quantitative and flexible manner. Relevance to listed research areas: This work is directly relevant to the Biological Threats and Countermeasures HS-STEM research area. It particularly addresses the assessment, characterization and prioritization of chemical-biological threats, and the medical response to biological threat events.

2. Tao Hong, Patrick Gurian, Nicholas Dudley Ward. "Analytical Equations Relating Aerosol Risk to Surface Concentrations," U.S. Department of Homeland Security University Network Summit and Student Day, Washington DC, March 2008.

Abstract:

Project Scope: In many cases human health risk from biological agents is associated with aerosol exposures. Environmental sampling conducted on surfaces can provide information about past and future aerosol risks presented by a biological agent. In this project, analytical equations are developed to relate the risk from aerosol exposure to the concentrations of spores on surfaces that could be sampled after a release. Recent Progress: Two scenarios are modeled. The first scenario assumes a release of aerosolized spores. This scenario is termed a retrospective risk scenario as the environmental samples would be used to infer past risk to occupants of the building. Analytical equations are developed to relate the past risk of mortality to the concentration of spores on four surfaces that could be sampled after the release 1) tracked floor, 2) untracked floor, 3) walls, 4) HVAC filters. These equations can be used to relate observed environmental concentrations to an allowable threshold for responding to risk. The second scenario assumes that the spores are initially on a tracked surface. This scenario is termed prospective risk, as environmental samples would be used to estimate future risk to occupants of the building. Analytical equations are again developed to relate risk to concentration of spores initially present on the tracked surfaces. Future Plans: In the future, we will focus on assessing the size distribution of aerosolized spores based on surface sampling results and identifying important uncertainties in the risk-sample relationships developed here. Relevance to listed research areas: This project is related to the area of Risk and Decision Sciences because it can provide guidance to incident response. By facilitating the estimation of risks, this work may assist responders in deciding whether response measures are justified, including vaccination and prophylactic treatment of exposed individuals, re-occupancy and decontamination of affected buildings.

3. Tao Hong, Patrick Gurian, Nicholas Dudley Ward. "Analytical Equations Relating Aerosol Risk to Surface Concentrations," The 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 2008.

Abstract:

Purpose of the study: In many cases human health risk from biological agents is associated with aerosol exposures. Environmental sampling conducted on surfaces can provide information about past and future aerosol risks presented by a biological agent. In this project, analytical equations are developed to relate the risk from aerosol exposure to the concentrations of spores on surfaces that could be sampled after a release. Methods used: Two scenarios are modeled. The first scenario assumes a release of aerosolized spores. This scenario is termed a retrospective risk scenario as the environmental samples would be used to infer past risk to occupants of the building. Analytical equations are developed to relate the past risk of mortality to the concentration of spores on four surfaces that could be sampled after the release 1) tracked floor, 2) untracked floor, 3) walls, 4) HVAC filters. The second scenario assumes that the spores are initially on a tracked surface. This scenario is termed prospective risk, as environmental samples would be used to estimate future risk to occupants of the building as a result of re-aerosolization. Analytical equations are again developed to relate risk to concentration of spores initially present on the tracked surfaces. Conclusion and future plan: For retrospective simulation, the risk of mortality can be linked with the concentration of anthrax on certain surface which creates a shortcut to estimating the risk level; for prospective simulation, the risk of mortality is related to the amount of anthrax released at the initial point when the dimension of room and type of anthrax is fixed. However, accurately measuring these risk levels, particularly for the smallest size fraction of B. anthracis (diameter of 1 µM), will be problematic. In the future, we will focus on assessing the size distribution of aerosolized spores based on surface sampling results and identifying important uncertainties in the risk-sample relationships developed here.

4. Mitchell-Blackwood, J., P.L. Gurian, and M.H. Weir. "Bayesian Hierarchical Modeling to Estimate Interspecies Dose-Response Safety Factors," The Joint U.S. Environmental Protection Agency and Department of Homeland Security Conference on Real-World Applications and Solutions for Microbial Risk Assessment, Bethesda, Maryland, April 2008.

Statement of Purpose: In this study, a Bayesian hierarchical statistical approach to fitting dose response parameters for Bacillus anthracis was compared to a classical, or frequentist, likelihood-based approach. The Bayesian approach uses a fully probabilistic framework to characterize parameter uncertainty. Parameters describing the susceptibility of individual species are modeled as deriving from a distribution describing the variation of susceptibilities among different species. This allows for estimates of the susceptibility of unobserved species to be determined based on species with observed susceptibilities. Statement of Methods Used: To assess the susceptibility of unobserved species on the basis of species with observed susceptibilities, a Bayesian meta-analysis is used to analyze experimental data from three different studies. The data obtained from open literature studies provided four sets of host-species/organism-strain groups for analysis as combined data using a hierarchical model. The single parameter exponential dose-response function was fit to the data. Parameters describing the susceptibility of individual species are modeled as deriving from a distribution describing the variation of susceptibilities among different species. Hyperparameters defined the prior distribution of the dose-response parameters for the population of host species and strains. Markov Chain Monte Carlo (MCMC) methods were used to develop posterior distributions of exponential dose response model parameters for each species. A sensitivity analysis on the prior distribution was conducted to evaluate its effect on the resulting posterior distributions. This is an important factor to evaluate when the sample size is small as is typical with dose-response studies. Summary of Results: When the risk vs. dose estimated for the mean parameter values generated by the Bayesian method are compared to those estimated by the maximum likelihood estimation (MLE) method, the curves are generally close. Deviations from the MLE curves are consistent with those expected by the influence of data from the other experiments. The Bayesian hierarchical model yields more narrow credible percentiles of risk when looking at the individual species. However, confidence intervals for the

unobserved species' dose-response from the Bayesian hierarchical model are much larger than for a classical approach, but the classical pooling process requires a much stronger assumption about the relatedness of humans and other species. Posterior distributions generated from both the informed and uninformed prior are similar, which indicates that specification of the prior assumption has little impact on the final predictions. Statement of Conclusions: The Bayesian hierarchical modeling approach reduces variance as more information is gained from the experimental data. Although the confidence intervals for unobserved species are much larger than those generated by the classical method, the Bayesian approach allows for quantification of the uncertainty associated with this extrapolation. Future work includes characterizing the degree of relatedness of different dose-response experiments for more accurate extrapolation to unobserved data sets, including humans. This work included looking at differences in Host/Species susceptibilities as well as Organism/Strain virulence. A reduction of uncertainty may be achieved by weighting the data sets of species closer to humans.

5. Mitchell-Blackwood, J., P.L. Gurian, and M.H. Weir. "A Hierarchical Model for Probabilistic Dose-Response Assessment of Bacillus anthracis," The Second Annual DHS University Network Summit, Washington, D.C., March 2008

    Abstract:

    Project Scope: To assess the susceptibility of unobserved species on the basis of species with observed susceptibilities, a Bayesian meta-analysis is used to analyze experimental data from three different studies. The data obtained from the studies provided four sets of host-species/organism-strain groups for analysis as combined data using a hierarchical model. Parameters describing the susceptibility of individual species are modeled as deriving from a distribution describing the variation of susceptibilities among different species. Hyperparameters defined the prior distribution of the dose-response parameters for the population of host species and strains. Markov Chain Monte Carlo (MCMC) methods were used to develop posterior distributions of exponential dose response model parameters for each species. A sensitivity analysis on the prior distribution was conducted to evaluate its effect on the resulting posterior distributions. This is an important factor to evaluate when the sample size is small as is typical with dose-response studies. Recent Progress: A Bayesian hierarchical statistical approach to fitting dose response parameters for Bacillus anthracis was compared to a classical, or frequentist, likelihood-based approach. The Bayesian approach uses a fully probabilistic framework to characterize parameter uncertainty. Confidence intervals for human dose-response from the Bayesian hierarchical model were much larger than for a classical approach, but the classical pooling process requires a much stronger assumption about the relatedness of humans and other species. Future Plans: A major challenge is to properly represent the degree of relatedness of different dose-response experiments. A framework for future research in this area is to consider two attributes for each experiment, microbial strain virulence and host species susceptibility. An autocorrelation function based on degree of difference on these attributes can then be used to represent the relatedness of different dose-response experiment in a quantitative and flexible manner. Relevance to listed research areas: This work is directly relevant to the Biological Threats and Countermeasures HS-STEM research area. It particularly addresses the assessment, characterization and prioritization of chemical-biological threats, and the medical response to biological threat events.

6. O'Donnell, C., P.L. Gurian, D. Scarsella and R. Johnson. "Threshold for Anthrax Vaccination," Drexel Research Day, April 22, 2008, 2008

    Abstract:

    The use of Bacillus anthracis (anthrax) in bioterrorism attacks is of concern in the wake of the 2001 terrorist attacks. Thus, it is necessary to prepare a contingency plan in case of such an attack. While vaccination is clearly justified for individuals exposed to substantial quantities of spores, there are

likely to be very large numbers of individuals exposed to very small quantities of spores. This study addresses the issue of whether such individuals should be vaccinated. A decision model was developed to assess the costs and benefits associated with vaccination. The risk of infection necessary to justify vaccination was then determined from the model. The environmental concentration corresponding to this threshold risk was estimated to be an exposure of 0.961 spores. Sensitivity analysis revealed that our decision model was not easily perturbed by changes in the cost of care of anthrax-induced illness.

7. Mitchell-Blackwood, J. and P.L. Gurian. "An Evaluation of the Risk Threshold for Prophylaxis and Treatment After An Anthrax Release," Drexel University Tenth Annual Research, Innovation, Scholarship and Creativity Day 2008, Philadelphia, PA, April 2008.

Abstract:

Abstract: Fowler et al. (2005) evaluated the cost-effectiveness of strategies for prophylaxis and treatment after an aerosolized release of B. anthracis under the scenario of a bioterrorism attack. The authors presented a decision analytic model to evaluate postattack response strategies: no prophylaxis, vaccination alone, antibiotic prophylaxis alone, or vaccination and antibiotic prophylaxis in combination, as well as preattack vaccination versus no vaccination. Their conclusion over a wide range of monetary values for a quality adjusted life year (QALY) was that postattack vaccination and antibiotic prophylaxis is the most effective and least costly alternative when compared to vaccination alone. However, the probability of infection used in their analysis was fixed at the high value 0.95 if no preventative action is taken. In reality, this risk of infection is variable based on the size of the release and/or the amount of exposure to which a person is subjected. At lower risk, the ï¿½??no actionï¿½?? alternative is therefore important to investigate. The purpose of this analysis is to conduct a sensitivity analysis on the probability of infection for Fowler et al.ï¿½??s preferred alternative in order to determine an acceptable threshold for administering antibiotics. The identification of a switchover point for which the no action alternative becomes preferred over postattack antibiotics is possible as well as when the no action alternative becomes preferred over all other alternative.

8. Tao Hong, Patrick Gurian, and Nicholas Dudley Ward. "Analytical Equations Relating Aerosol Risk to Surface Concentrations". Tenth Annual Research Day at Drexel University, Philadelphia, PA, U.S.A.(2008).

Purpose of the study: In many cases human health risk from biological agents is associated with aerosol exposures. In order to correctly interpret environmental samples conducted on surfaces which can provide information about past and future aerosol risks presented by a biological agent, there is a threshold for sampling area. In this project, analytical equations are developed to relate the risk from aerosol exposure to the concentrations of spores on surfaces that could be sampled after a release and calculate minimum sampling area for correctly interpreting samples. Methods used: Two scenarios are modeled. The first scenario assumes a release of aerosolized spores. This scenario is termed a retrospective risk scenario as the environmental samples would be used to infer past risk to occupants of the building. Analytical equations are developed to a) relating the past risk of mortality to the concentration of spores on four surfaces (1. tracked floor, 2. untracked floor, 3. walls, 4. HVAC filters) that could be sampled after the release b) estimating the minimum sampling area which could correctly interpret samples. The second scenario assumes that the spores are initially on a tracked surface. This scenario is termed prospective risk, as environmental samples would be used to estimate future risk to occupants of the building as a result of re-aerosolization. Analytical equations are again developed to estimate minimum sampling area and relate future risk to concentration of spores initially present on the tracked surfaces. Conclusion and future plan: For retrospective simulation, the risk of mortality can be linked with the concentration of anthrax on certain surface which creates a shortcut to estimating the risk level; for prospective simulation, the risk of mortality is related to the amount of anthrax released at the initial point when the dimension of room and type of B. anthracis is fixed. The minimum sampling area has a inverse proportion relation to surface concentration and particle diameter, which

indicates that accurately measuring these risk levels for the smallest size fraction of B. anthracis (diameter of 1 ÂμM), will be problematic. In the future, we will focus on assessing the size distribution of aerosolized spores based on surface sampling results and identifying important uncertainties in the risk-sample relationships developed here.

9. Madsen, J. and P.L. Gurian. 2008. "A Valuation of the BioWatch Detection System." Tenth Annual Research Day at Drexel University, Philadelphia, PA, USA.

Abstract:

The Centers for Disease Control and Prevention classify Bacillus anthracis as a Category A biological agent. Its potential for devastating an urban setting and its use as a terrorist weapon in the past have led to development of a federally supported environmental detection system known as BioWatch. This system is designed to decrease the time to detection in the event of a B. anthracis release, reducing costs in prophylaxis of exposed persons as well as quality-adjusted-life-years (QALYs) and treatment of persons contracting inhalational anthrax. Objective: To determine the value of the BioWatch program for a single urban area in a year. Method: A decision analytic model is constructed to estimate benefits and cost with and without the BioWatch program. A sensitivity analysis is conducted to estimate the value of the BioWatch program. Data Sources: Costs and probabilities are taken from medical and emergency preparedness literature, as well as estimates from experts in the field. Target Population: People living or working in a large American city. Results of Base-Case Analysis: The BioWatch system is valued at $32.3 million per year, per large city. This value does not take into consideration the system's capacity for detection of other biological or chemical agents, the list of which is classified. Sensitivity Analysis: Depending on the assumed value of one QALY, the program may not be cost-effective. Conclusion: Based on limited information available regarding cost of running the BioWatch program, it is cost-effective, even if only for detection of a large B. anthracis release.

10. Jade Mitchell-Blackwood, Tao Hong, Nicholas Dudley Ward, Patrick L. Gurian, "Relating Human Health Risk to Environmental Concentrations of B. anthracis using Analytic Models," 11th Annual Force Health Protection Conference, Albuquerque, NM, 9 - 15 August 2008.

Abstract:

The need to relate environmental concentrations of B. anthracis to human health risk in order to make decisions about the administration of vaccines and antibiotics, as well as to determine acceptable clean-up standards is well established. Environmental sampling can provide information about aerosol risks even though air concentrations of the agent rapidly decay after a release. In this work, analytical equations were developed based on the mass balance relationship in an office suit to relate concentrations of B. anthracis to risk. A Bayesian hierarchical approach was used to generate estimates and safety factors for humans based on non-human data from experiments linking inhaled dose to risk of mortality. A decision analytic model was also evaluated using costs and utility metrics to identify the risk level at which the decision to provide treatment in the event of an attack becomes justified at a certain probability of infection.

11. Yin Huang, Tao Hong, Timothy Bartrand, Patrick L. Gurian, Charles N. Haas, Ran Liu and Sushil Tamrakar "How Sensitive is Safe? Risk-based Targets for Ambient Monitoring of Pathogens," 2008 International Symposium on Spectral Sensing Research, Hoboken, NJ, 23 – 27 June, 2008

Abstract:

Biological agents present hazards at concentrations far below those of concern for most chemical agents. Detecting such low concentrations poses a great challenge to environmental monitoring systems. This study proposed a framework to address the questions of 1) what level of risk would trigger the use of such countermeasures, 2) what environmental concentrations would have to be detected to identify the target risk level. In the first part of the framework, a decision model is developed to assess the costs and benefits of prophylactic antibiotic treatment for Y. pestis as a function of the risk of illness. A sensitivity analysis is then conducted to identify a threshold level of risk at which medical treatment of exposed individuals is justified. Risk levels of 5×10^{-5} are estimated to be sufficient to justify treatment of exposed individuals. A dose-response function for rodents, based on intra-peritoneal exposure is developed to map these risk levels to delivered doses to individuals. Estimates are that an average dose of 4 organisms is sufficient to trigger medical treatment for an exposed population. A range of human breathing rates are used to estimate the air phase concentrations corresponding to this dose over an 8-hour exposure period. Adjustments to this value to reflect removal in the upper respiratory track may be appropriate. Corresponding air phase concentrations for smallpox are two orders of magnitude lower than for Y. pestis, while those for B. anthracis are an order of magnitude higher, possibly because the dose-response model is fit to primates exposed by the inhalation route. These air phase concentrations represent idealized goals for the sensitivity of detector systems. By linking environmental concentrations to goals for detection, this paper provides a framework for assessing the sensitivity of novel sensing systems and which can also inform the interpretation of negative results from such systems.

4. Organization of workshops:

   Gurian, P. "Statistical Analysis with the R Programming Language," Society for Risk Analysis Meeting, San Antonio, Texas, December 2007.

5. Participation in workshops:

   Gurian, P. presented at Quantitative Microbial Risk Assessment (QMRA) Workshop, 108th American Society for Microbiology General Meeting, June 2008, Boston, MA.

   Gurian, P. "Statistical Analysis with the R Programming Language," Society for Risk Analysis Meeting, San Antonio, Texas, December 2007.

   Gurian, P. "Statistics and Uncertainty," Quantitative Microbial Risk Assessment Summer Institute, Michigan State University, August, 2008.

   Gurian, P. "Risk Perception, Communication, and Management," Quantitative Microbial Risk Assessment Summer Institute, Michigan State University, August, 2008.

6. Case studies:

   An approach to identifying appropriate risk levels for undertaking response actions has been developed and applied to plague. Efforts to apply this method to anthrax are in progress.

7. Algorithms developed:

   Work on an environmental persistence model selection algorithm is in progress in collaboration with Project I.

8. Human Resource Development:

A total of 6 students are working in conjunction with this project (2 doctoral and 4 MPH), supported by CAMRA funds and/or fellowship funds.

9. Funds Leveraged (additional funding. resources for free):

A $490,000 grant has been obtained from the Department of Homeland Security to provide fellowships to masters students in microbial risk assessment. Four students are currently supported by this grant in whole or in part and are contributing to CAMRA research: April Wright, Cara O'Donnell, Rachel Johnson, and John Madsen.

Jade Blackwood obtained a GAANN fellowship for the 2007-2008 academic year. This provided $22,600 in stipend and $12,224 in tuition. She also obtained an ORISE internship which supported her during the summer She has obtained a GK-12 fellowship for the 2008-2009.

2. Outcomes (how your contributions can be used to better society):

The results of this project are intended to allow environmental sampling results to be related to risk so that in the event of a release, responders can make informed decisions about where clean up efforts should be performed. This includes guidance for air and surface sampling. Because microbial pathogens may be of concern at very low environmental concentrations, specific guidance for sampling area and volumes are being developed so that negative results can appropriately be interpreted as indicating that risks are below levels of concern.

3. Integration with other projects (association between units in different projects):

Project IV investigators worked with Project III investigators to develop risk-based targets for air sampling efforts. This collaboration led to a poster presentation and a manuscript which is under review by the *IEEE Sensors Journal*. Project IV continued to work with Project III to identify appropriate data sets for Bayesian Hierarchical dose response modeling. In addition to the anthrax datasets identified in previous years, several tularemia datasets were identified this year.

Project IV investigators have previously identified HVAC filters as a key location for environmental sampling. Laboratory work is being explored in conjunction with Project I investigators to quantify the recovery of surrogate spores from HVAC filters.

Project IV is also working with Project I to develop a spreadsheet tool for the analysis of environmental persistence data.

4. Tasks for Next Year: IV (Sep 15 2008 to Sep 14 2009)

10. Complete an M.S. thesis on the development of relationships between environmental concentrations and risk.
11. Complete manuscript on risk at which response to *B. anthracis* exposure becomes justified by benefit-cost analysis.
12. Complete manuscript on Bayesian hierarchical modeling of interspecies/interstrain effects.

5. Anticipated Technical Results and Developments (examples of potential learning units for next year, within possible also include potential outcomes):

The M.S. thesis work described in Task 1 above may need to be extended to address non-persistent agents. The work with Project I developing a standard tool for persistence analysis may facilitate further data analysis and

publications, including a meta-analysis of persistence of microbes in the environment.

References

Fowler, R.A., G. D. Sanders, D. M. Bravata, B. Nouri, J. M. Gastwirth, D. Peterson, A. G. Broker, A. M. Garber, and D. K. Owens, "Cost-effectiveness of defending against bioterrorism: A comparison of vaccination and antibiotic prophylaxis against anthrax," *Ann Intern Med.,* vol. 142, pp. 601-610, 2005.

Sextro, R.G., D.M. Lorenzetti, M.D. Sohn, and T.L. Thatcher, "Modeling the spread of anthrax in buildings," *Proc. of Indoor Air 2002 Conf.,* 2002.

CAMRA Report for Year III (Sep 15 2007 to Sep 14 2008) for Project 4

1. Project 4, Project IV
2. Investigators: Elizabeth Casman,
3. Project Goals (from proposal, additional goals):

    APG: The goal of this task is to understand how public perception of influenza transmission affects exposure and mitigative response behaviors by the public, and to identify key misunderstandings that could be corrected with targeted risk communications.
    APM: Analysis of semi-structured interviews
    Outcome: Practical guidance to inform risk management decisions that must be made in preparation for and in response to pandemic influenza.

4. Tasks for Year III (Sep 15 2007 to Sep 14 2008):

    a. Recruit of 40 subjects (30 general public, 10 high risk occupation)
    b. Conduct semi-structured phone interviews according to tested protocol developed in year 2
    c. Transcribe interviews

5. Research Activities
    Investigating mental models

6. Background and prior research (from learning units of the type Things I have read, those essential references you want to include; from Year II, include summary of previous years):

7. Mental models of influenza transmission (206,207)
    Things that are in progress LU 206
    Author(s): Elizabeth Casman
    and Things that I have completed LU 207
    Author(s): Elizabeth Casman
    When Investigating mental models of influenza transmission we wanted to find out whether people have erroneous concepts and if there are gaps in their knowledge that should be addressed by risk communication
    Experimental Design was as follows:
    a. Recruited of 40 subjects (30 general public, 10 high risk occupation) b. Conducted semi-structured phone interviews according to tested protocol developed in year 2 c. Transcribed interviews, d. coded transcribed interviews
    Contribution:
    These tasks produced a database that allows us to analyze the interview responses
    Results:
    Project is on target for completion on schedule. The focus of this work is to improve risk communication

for a homeland security priority scenario.

8. Outputs:
    1. Students Supported:
    2. Students Graduated:
    3. Publications:
    Paper "Risk Communication Planning for the Aftermath of a Plague Bioattack. Risk Analysis,"
    Vol. 28, No. 4, 2008, 1327-41. ABSTRACT: We create an influence diagram of how a plague
    bioattack could unfold and then use it to identify factors shaping infection risks in many possible
    scenarios. The influence diagram and associated explanations provide a compact reference that
    allows risk communicators to identify key messages for pre-event preparation and testing. It can
    also be used to answer specific questions in whatever unique situations arise, considering both the
    conditions of the attack and the properties of the attacked populations. The influence diagram
    allows a quick, visual check of the factors that must be covered when evaluating audience
    information needs. The documentation provides content for explaining the resultant advice. We
    show how these tools can help in preparing for crises and responding to them.
    Accomplishments by Elizabeth Casman
    Paper "Threshold conditions for bubonic plague persistence in urban rats" submitted to PNAS in
    Sep 2008 ABSTRACT: In this paper we derive 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.
    Accomplishments by Elizabeth Casman
    Patents:
    4. Presentations:
    "Plague Dynamics in Urban Rodents," D. Durham and E. Casman, Joint U.S. Environmental
    Protection Agency and Department of Homeland Security Conference on Real-World
    Applications and Solutions for Microbial Risk Assessment, April 8-10, 2008, Bethesda, MD.
    Accomplishments by Elizabeth Casman
    "Risk Communication Planning for the Aftermath of a Plague Bioattack" E. Casman, Joint U.S.
    Environmental Protection Agency and Department of Homeland Security Conference on Real-
    World Applications and Solutions for Microbial Risk Assessment, April 8-10, 2008, Bethesda,
    MD.
    Accomplishments byElizabeth Casman
    "Should We Worry About Plague in Urban Rats in the U.S." D.P. Durham & E.A. Casman,
    Society for Risk Analysis Annual Meeting, December 2007, San Antonio. (winner of best student
    paper in Ecology award)
    Accomplishments by Elizabeth Casman

    5. Organization of workshops:

    6. Participation in workshops:
    DHS July 22-25, 2007, Cambridge, MD
    Department of Homeland Security Risk Perceptions and Communications Conference, July 22-25,
    2007, Cambridge, MD.
    Accomplishments byElizabeth Casman
    7. Case studies:
    8. Algorithms developed:
    Derived an algebraic expression for threshold condition for plague persistence in rats.
    Accomplishments by Elizabeth Casman
    9. Human Resource Development:

10. Funds Leveraged (additional funding. resources for free):
    Funding for graduate student David Durham was obtained from the MacArthur Foundation.
    Accomplishments by Elizabeth Casman
9. Outcomes (how your contributions can be used to better society):
    Unit 207: Dataset of concepts identified by interview subjects
10. Integration with other projects (association between units in different projects):

Project II provided feedback on expert model development.

11. Tasks for Next Year: IV (Sep 15 2008 to Sep 14 2009)
    Coding and analysis

    Develop a web survey

12. Anticipated Technical Results and Developments (examples of potential learning units for next year, within possible also include potential outcomes):

    Write a paper summarizing findings

CAMRA Report for Year III (Sep 15 2007 to Sep 14 2008) for Project 5

1. Project 5, Project V
2. Investigators: Rosina Weber, Sidath Gunawardena , XuNing Tang
3. Project Goals (from proposal, additional goals):
    1. Build a web-based knowledge repository to support sharing and leveraging for the CAMRA research community.
    2. 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 III (Sep 15 2007 to Sep 14 2008):

    1. Complete design and implementation of Version 2.0.

        a. Complete design of Search

        b. Complete design of Reporting

        c. Complete design of Visualization

        d. Merge all learning units from version 1.0 to Version 2.0

    2. Apply survey and conduct analysis before Version 2

    3. Launch Version 2.0 Beta and conduct Usability test

    4. Revise and launch Stable Version 2.0

    5. Apply survey and conduct analysis after Version 2

    6. Reason with learning units for knowledge discovery

5. Research Activities

Designing search
Designing CAMRA KR
Testing CAMRA KR
Implementing CAMRA KR
Designing artifacts
Designing knowledge repository

6. Background and prior research (from learning units of the type Things I have read, those essential references you want to include; from Year II, include summary of previous years):

7. Research Contributions this Year (how you advanced MRA, contributions and results from completed learning units; please list the numbers of the learning units, as follows:

CAMRA KR Version 2.0: Designing of Visualization Things that are in progress LU (222)
Author(s): Rosina Weber
When Designing CAMRA KR we wanted to find out a method for visualizing knowledge artifacts contained in a controlled repository
Experimental Design was as follows:
determine attributes and associations to be visualized survey types of visualizations available select type of visualization best suited for needs of CAMRA KR users construct visualizations of knowledge artifacts using Prefuse integrate coding with CAMRA KR Version 2.0 test visualization

CAMRA KR Version 2.0: Testing Things that are in progress LU (226)
Author(s): Rosina Weber
When Testing CAMRA KR we wanted to find out whether there are any bugs or deficiencies in CAMRA Version 2/0
Experimental Design was as follows:
Perform unit tests of standalone modules of CAMRA KR Version 2.0 Perform integration test of all modules of CAMRA KR Version 2.0 Perform acceptance tests of CAMRA KR 2.0

CAMRA KR Version 2.0: Implementation Things that are in progress LU (228)
Author(s): Rosina Weber
When Implementing CAMRA KR we wanted to find out Trying to obtain the implemented stable version of CAMRA KR Version 2.0
Experimental Design was as follows:
Implement Reporting Functionality Implement Search Functionality Implement Commenting Functionality Implement Visualization Functionality

Designing search for CAMRA KR Version 2.0 (58,59)
Author(s): Rosina Weber
When Designing search we wanted to find out What the most effective search method for learning units is
Experimental Design was as follows:
We will compare case-based reasoning methods to assess similarity with more traditional methods to retrieve useful documents.
Contribution:
The most effective method to retrieve useful learning units is the horizontal representation with the recommended cardinality factor (RCF), which recommends to users how many terms to enter when creating a query.

Results:
Retrieval using horizontal representation with RCF resulted more accurate then comparable methods in the presence of incomplete data, i.e., knowledge artifacts of variable length

CAMRA KR Version 2.0: Designing of Reporting (223,225)
Author(s): Rosina Weber
When Designing CAMRA KR we wanted to find out an algorithm for generating automated reports from knowledge artifacts contained in an controlled repository
Experimental Design was as follows:
analyze associations between units design algorithm leveraging learning unit representation and associations to generate reports compare automatically generated reports to user created reports obtain feedback on automatically generated reports from users and funding agency representatives integrate report generation algorithm into CAMRA KR Version 2.0 test reporting functionality
Contribution:
using the representation of the knowledge artifacts and the associations between them, it is possible to automatically generate reports that meet the needs of the funding agencies
Results:
An algorithm was designed to automatically generate reports from learning units

Designing CAMRA KR Version 2.0 (236,237)
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:
esign version 2.0 of the knowledge repository based on - feedback from CAMRA members of their experiences - feedback from funding agencies - recommendations from HCI experts
Contribution:
The combination of the structure and the retrieval method produces an adequate strategy for knowledge sharing that guides targeted users toward best results
Results:
we designed a structure to represent and a method to retrieve knowledge artifacts for repository-based knowledge management systems

Designing CAMRA KR Version 2.0 (236,239)
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:
esign version 2.0 of the knowledge repository based on - feedback from CAMRA members of their experiences - feedback from funding agencies - recommendations from HCI experts
Contribution:
a framework to develop Knowledge Management Systems that can perform multifunctional tasks in one single architecture
Results:
a knowledge management framework that follows principles from knowledge engineering and from the management literature on how to prevent failure in KMS presents

8. Outputs:
   1. Students Supported:

Supported Doctortal Student (Sidath Gunawardena, Drexel University)
Sidath Gunawardena, doctoral student, Drexel University
Accomplishments by Rosina Weber

2. Students Graduated:
3. Publications:
Horizontal Case Representation Paper
Weber, R. O., Gunawardena, S. & MacDonalds, C. (2008). Horizontal Case
Representation. In K.-D. Althoff et al. (Eds.), Advances in Case-Based Reasoning:
Proceedings of the European Conference on Case-Based Reasoning (ECCBR 2008);
LNAI 5239 (pp. 548-5
Accomplishments byRosina Weber
Multifunctional Knowledge Management Systems paper
Weber, R. O. & Gunawardena, S. (2008). Designing Multifunctional Knowledge
Management Systems. Proceedings of the 41st Annual Hawaii International Conference
on System Sciences (HICSS-41), Jan. 2008 Page(s):368 - 368.
Accomplishments byRosina Weber
Representing and Retrieving Knowledge Artifacts. paper
Weber, R. O., Gunawardena, S. & Abraham, G. (2008). Representing and Retrieving
Knowledge Artifacts. T. Yamagchi (Ed.): PAKM 2008, 2008, LNAI 5345, pp. 86-97,
2008. Â© Springer-Verlag Berlin Heidelberg 2008
Accomplishments byRosina Weber

4. Patents:
5. Presentations:
The CAMRA Knowledge Management Approach
Weber, R. O. & Gunawardena, S. (2008). The CAMRA Knowledge Management
Approach. Poster presented at The Joint U.S. Environmental protection Agency and
Department of Homeland Security Conference on Real World Applications and Solutions
for Microbial Risk Assessment. Bethesda North Marriott Hotel and Conference Center,
North Bethesda, Maryland. April 8-10, 2008
Accomplishments byRosina Weber

Discovering Optimal search Term Cardinality
Gunawardena, S., MacDonalds, C., & Weber, R. O. & (2008). Discovering Optimal
search Term Cardinality. Poster presented at The Joint U.S. Environmental protection
Agency and Department of Homeland Security Conference on Real World Applications
and Solutions for Microbial Risk Assessment. Bethesda North Marriott Hotel and
Conference Center, North Bethesda, Maryland. April 8-10, 2008. Abstracts available
online at: http://www.scgcorp.com/epahomelandsec/abstracts.asp
Accomplishments byRosina Weber

6. Organization of workshops:
7. Participation in workshops:
8. Case studies:
9. Algorithms developed:
10. Human Resource Development:
11. Funds Leveraged (additional funding. resources for free):

9. Outcomes (how your contributions can be used to better society):Unit 58: A validated search
method to be used with learning units
Unit 59: A validated search method to be used with learning units
Unit 222: CAMRA users can see how their research integrates with other projects
Unit 223: CAMRA users will spend less time and effort in generating reports.
10. Integration with other projects (association between units in different projects):There were no
research collaborations between members of Project Project V and other projects.
11. Tasks for Next Year: IV (Sep 15 2008 to Sep 14 2009)
12. Anticipated Technical Results and Developments (examples of potential learning units for next

year, within possible also include potential outcomes):

References

[1]   Weber, R. O. & Gunawardena, S. (2008). The CAMRA Knowledge Management Approach. Poster presented at The Joint U.S. Environmental protection Agency and Department of Homeland Security Conference on Real World Applications and Solutions for Microbial Risk Assessment. Bethesda North Marriott Hotel and Conference Center, North Bethesda, Maryland. April 8-10, 2008
[2]   Weber, R. O., Morelli, M. L., Atwood, M. E., Proctor, J. M. (2006) Designing a Knowledge Management Approach for the CAMRA Community of Science. In: U. Reimer and D. Karagiannis (Eds.): PAKM 2006, LNAI vol. 4333, pp. 315–325. © Springer-Verlag Berlin Heidelberg 2008
[3]   Weber, R. O., Gunawardena, S. & Abraham, G. (2008). Representing and Retrieving Knowledge Artifacts. T. In: Yamagchi (Ed.): PAKM 2008, LNAI 5345, pp. 86-97. © Springer-Verlag Berlin Heidelberg 2008
[4]   Gunawardena, S., MacDonald, C., & Weber, R. O. (2008). Discovering Optimal search Term Cardinality. Poster presented at The Joint U.S. Environmental protection Agency and Department of Homeland Security Conference on Real World Applications and Solutions for Microbial Risk Assessment. Bethesda North Marriott Hotel and Conference Center, North Bethesda, Maryland. April 8-10, 2008. Abstracts available online at: http://www.scgcorp.com/epahomelandsec/abstracts.asp
[5]   Weber, R. O., Gunawardena, S. & MacDonald, C. (2008). Horizontal Case Representation. In: K.-D. Althoff et al. (Eds.): ECCBR 200), LNAI 5239 pp. 548-562. © Springer-Verlag Berlin Heidelberg 2008
[6]   Weber, R. O. & Gunawardena, S. (2008). Designing Multifunctional Knowledge Management Systems. Proceedings of the 41st Annual Hawaii International Conference on System Sciences (HICSS-41), pp. 368 - 368.
[7]   Weber, R. O., Gunawardena, S. and Proctor, J. M. "Generating Reports from Case-Based Knowledge Artifacts," in Proceedings of the Twentieth International Florida Artificial Intelligence Research Society, D. Wilson and G. Sutcliffe, Eds. Menlo Park, CA: AAAI Press, 2007.

CAMRA Report for Year III (Sep 15 2007 to Sep 14 2008) for Integration (Projects I-V)

1. Integration (Projects I-V): Applying and Transfer of CAMRA Knowledge
2. Investigators: Joan B. Rose, Tomoyuki Shibata, Yoshifumi Masago, S. Devin McLennan
3. Project Goals (from proposal, additional goals):

   - Applying CAMRA's knowledge to real world investigations
   - Transferring CAMRA knowledge to public by organizing workshops
   - Assisting co-directors in managing CAMRA research activities as well as communications within and outside CAMRA.

4. Tasks for Year III (Sep 15 2007 to Sep 14 2008):

   - 3rd CAMRA Microbial Risk Institute summer workshop
   - Develop Manual for QMRA
   - Develop Newsletter "Perspectives in Microbial Risk"

5. Research Activities
   Collecting data
   Organizing meetings
   Presenting workshops
   Teaching quantitative microbial risk assessment
   Creating risk assessments

6. Background and prior research (from learning units of the type Things I have read, those essential references you want to include; from Year II, include summary of previous years):

7. Research Contributions this Year (how you advanced MRA, contributions and results from completed learning units; please list the numbers of the learning units, as follows:

CAMRA Fomite Matrix Things that are in progress LU (156)
Author(s): S. Devin McLennan
We wanted to gather all CAMRA fomite data into a single data file to facilitate comparative analysis. Completing this matrix of fomite data illustrates the differences and similarities between fomite studies, highlighting overall trends, revealing data gaps, and serving as a guide for further research and the development of standard methods.
Experimental Design was as follows:
Fomite data sets generated by CAMRA investigators were gathered and combined into a single spreadsheet listing all experimental conditions, graphed as a function of each variable, and analyzed for simple linear trends. This preliminary analysis has been made available to all CAMRA fomite researchers for further investigation.

3rd QMRA Summer Institute (346,347)
Author(s): S. Devin McLennan
In this workshop we wanted to provide participants with the necessary skills to engage in quantitative microbial risk assessment.
Experimental Design was as follows:
Presented lectures on the components of QMRA, gave practice exercises on relevant computer, mathematical, and reasoning tools, lead participants through one of four case studies.
Contribution:
Interdisciplinary teams of participants studied and practiced QMRA
Results:
The following presentations and exercises were conducted at the 3rd QMRA Summer Institute, Michigan State University, East Lansing, MI, August 10-15, 2008.
 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
 Haas, CN, Weir, M : Monte-Carlo Simulation
 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
CAMRA CASE STUDIES 2008 3rd QMRA Institute
 A. Anthrax release: led by Chuck Haas
 B. Norovirus Outbreaks: led by Mark Weir
 C. Tularemia in Water: led by Joan Rose & Gertjan Medema
 D. Bird Influenza: led by Patrick Gurian
Case Study Objectives: to develop a microbial risk framework that addresses real world problems that require an integration of data and information in order to assess, manage and communicate

microbial and infectious disease risks from intentional or accidental contamination of the built and natural environment. Specific goals 1. Develop and describe a Microbial Risk Framework (problem, hazard(s), dose-response, exposure pathways, individual and population risk characterization) 2. Identify data & data needs 3. Identify Techniques & models 4. Identify Assumptions 5. Undertake a quantitative microbial risk assessment 6. Develop conclusions on risk 7. Identify data gaps 8. Describe potential management approaches or decision-support systems needed

Anthrax Case Study, 3rd QMRA Summer Institute (346,350)
Author(s): S. Devin McLennan
Contribution:
Students and professionals from multiple science and engineering disciplines used QMRA tools taught in the Summer Institute to produce a quantitative microbial risk assessment for an anthrax release in a government office.
Results:
Anthrax release Background: Since the 9/11 anthrax attacks associated with powdered and aerozolizable spore preparations, more interest has been paid to the need to establish sampling protocols and estimates of risk which can then be followed by clean up strategies for surfaces. Bacillus anthracis is a very resistant organism, which can survive in the environment for extended periods of time. It●??s use as a biological weapon has a long history but only recently has a dose-response model been available. Anthrax spores cause high mortality if inhaled (75%) or ingested (20 to 60%) if no antibiotic treatment is used. The spores are very robust in the environment, and will survive for long periods of time on surfaces. The ability to sample the environment after an attack and determine the risk may be critical to establishing clean up goals. However methods may not be adequate for determining acceptable risk. Current dose-response models are available and will.
Problem: A package containing anthrax spores is opened in an office (30 ft by 40 ft with 5 desks) and is quickly aerosolized and dispersed. It is 30 minutes before the hazard is recognized and personnel are evacuated. Environmental sampling is needed What statistical approach would you take to gather quantitative information on the potential exposure? What is the risk per person you estimate from the exposure? What level of risk could be determined with the various methods? What are the considerations regarding exposure? What would be your clean up target? What are the key uncertainties in the risk estimate? What research is needed to improve the risk estimate? How would you communicate the risk?

Norovirus Case Study, 3rd QMRA Summer Institute (346,352)
Author(s): S. Devin McLennan
Contribution:
Students and professionals from multiple science and engineering disciplines used QMRA tools taught in the Summer Institute to produce a quantitative microbial risk assessment of Norovirus outbreaks on rental houseboats.
Results:
Norovirus Outbreaks: Background: Noroviruses (NoVs) are one of the major causes of outbreaks world-wide. In the US alone 23 million cases of illness are reported annually. Outbreaks are occurring in venues where large numbers of people become ill including restaurants, cruise ships, schools and nursing homes. Most recently several deaths have been associated with the virus infection. Many of these outbreaks are large, are extremely costly to the economic well-being of the food and tourism industries. The deaths in the elderly in particular demonstrate the growing impact this type of pathogen will have on health care as populations and indeed the world ages. This virus is spread by viral-laden feces and vomitus and then via surfaces, water, food and hands. NoVs are RNA viruses which have only recently been cultivated in cell culture (Straub TM, Honer zu Bentrup K, Orosz-Coghlan P, Dohnalkova A, Mayer BK, Batholomew RA, et al. In vitro cell culture assay for human noroviruses. Emerg Infect Dis. 2007;13:396-403. Available from http://www.cdc.gov/eid/content/13/3/396.htm But most of the detection is by RT-PCR (reverse transcription- polymerase Chain reaction) a molecular technique which identified specific genes. The contamination is generally wide-spread and is difficult to clean up. Addressing via a science-

based risk framework the challenges of this virus will assist in the understanding and management of other viruses such as Bird Flu, and potentially smallpox should an intentional terrorist event occur.

Problem: Cruise ships are notorious venues for propagating norovirus outbreaks. A recent outbreak on a houseboat demonstrated that environmental contamination lead to the disease cases in the following group that used the boat. Thus clean up was not adequate. In addition, a dose-response model has not be readily available. Can a risk dose-response model be developed from recent human feeding studies? Can this dose-response model be used to elucidate transmission risks based on the epidemiological data? What was the role of fomites in disease transmission in the outbreak on the house boat? Can the Dose-response be used to define exposures and contrasted to other viruses and attack rates ? What prevention strategies can be used in the future? What level of disinfection is required to be safe? What are the key uncertainties in the risk estimate? What research is needed to improve the risk estimate? How would you communicate the risk?

Tularemia Case Study, 3rd QMRA Summer Institute (346,354)
Author(s): S. Devin McLennan
Contribution:
Students and professionals from multiple science and engineering disciplines used QMRA tools taught in the Summer Institute to produce a quantitative microbial risk assessment of a release of the bioterrorist agent Tularemia into a water distribution system, based on an actual scenario involving Cryptosporidium.
Results:
Tularemia in Water: Background Water-borne outbreaks continue to occur in the developed world. At greatest risks are waters which do not carry a disinfectant residual, such as wells or many distribution systems. Many etiological agents have been identified during outbreaks these include Cryptosporidium, which is very resistant to chlorine and viruses as well as bacteria including Salmonella, and Vibrio. In many cases the epidemiological curves during outbreaks as well as attack rates can be examined to better understand the exposure pathways and approaches for control.

Problem: Recently in Northhamptonshire in the UK a rabbit was found to be the source of a Cryptosporidium outbreak. As previously reported by WaterTech Online, the outbreak affected 100,000 homes and sickened 13 people. It was suggested that it may have been planted there on purpose, according to a July 18 article in the Lutterworth Mail. How could one develop a quick approach using symptomology to begin to define the etiological agent? Given different attack rates how would you define the exposure from the dose-response curve? If the rabbit was infected with Tularemia, a bioterroist agent what would be the risk? What would be the risk from inhalation (during a shower) compared to ingestion? What level of disinfection is needed to control the risk? What are the key uncertainties in the risk estimate? What research is needed to improve the risk estimate? How would you communicate the risk?

Avian Influenza Case Study, 3rd QMRA Summer Institute (346,356)
Things that are in progress LU 346
Contribution:
Students and professionals from multiple science and engineering disciplines used QMRA tools taught in the Summer Institute to produce a quantitative microbial risk assessment of an infected bird smuggled into an airport customs checkpoint.
Results:
Risks associated with Bird Influenza: Background: Through out the globe human cases of avian influenza A (H5N1) have been reported in Asia, Africa, the Pacific, Europe and the Near East with the greatest number of cases in Indonesia and Vietnam Mortality in humans with H5N1 is approximately 60%. Studies have documented the most significant risk factors for human H5N1 infection to be direct contact with sick or dead poultry or wild birds, or visiting a live poultry market.

Problem: Border officers may be at risk of acquiring bird influenza infections as they inspect poultry. During inspection of crested eaglets by Brussels CBP officers, that had been transported in wicker tubes from Asia, the birds were shown to have avian influenza H5N1. The birds were

confiscated and humanely sacrificed, no human cases of H5N1. What is the risk of infection given different dose-response functions? What is the lag time (time between exposure, infections and symptoms) and time that an individual may remain infectious?. What type of secondary transmission rates could lead to a pandemic? What methods are most effective at reducing risk? What are the key uncertainties in the risk estimate? What research is needed to improve the risk estimate? How would you communicate the risk?

1-day QMRA Workshop at ASM 2008 General Meeting (347,382)
Author(s): S. Devin McLennan
Interdisciplinary teams of participants attended lectures and conducted practice exercises to gain basic skills in QMRA.
The goal of this workshop was to provide QMRA information to professional microbiologists.
The current Experimental Design is as follows:
The workshop included lectures and exercises illustrating the core concepts of QMRA.

8. Outputs:
   1. Students Supported:
   2. Students Graduated:
   3. Publications:
   Bacteriophage P22 and Staphylococcus aureus Attenuation on Nonporous Fomites as Determined by Plate Assay and Quantitative PCR
   Yoshifumi Masago, Tomoyuki Shibata, and Joan B. Rose. 2008. Bacteriophage P22 and *Staphylococcus aureus* Attenuation on Nonporous Fomites as Determined by Plate Assay and Quantitative PCR. Applied and Environmental Microbiology 74(18):5838-5840. Abstract: Decay rates of bacteriophage P22 and Staphylococcus aureus on six types of common household inanimate surfaces were evaluated based on cultivation and quantitative PCR. A much higher level of inactivation was observed using the plate assay, suggesting that detection of the pathogen genome in samples from fomites does not necessarily imply a health risk to humans.
   Accomplishments by S. Devin McLennan

   Instruction Manual for Quantitative Microbial Risk Assessment (QMRA)
   Rose, J. B., C. N. Haas, P. L. Gurian, and J. S. Koopman. 2008. Instruction manual for quantitative microbial risk assessment (QMRA). CAMRA 3rd QMRA Summer Institute, Michigan State University, East Lansing, MI.
   Accomplishments by S. Devin McLennan

   4. Patents:
   5. Presentations:
   Anthrax Release Case Study for 3rd QMRA Summer Institute
   Herzog, A., C. Rodriguez, K. Enger, M. Milbrath, O. Bucher, P. Okelo, S. Luster-Teasley, and Y. Huang. 2008. Risk Assessment: Release of Anthrax in an IRS Building. Group A Case Study: CAMRA 3rd QMRA Summer Institute, Michigan State University, East Lansing, MI.
   Accomplishments by S. Devin McLennan

   Norovirus Case Study for 3rd QMRA Summer Institute
   Pandey, A., W. Betacourt, A. Baynton, A. Wright, K. Bush, S. Khan, K. Shaw, A. Coulliette. 2008. Adventure Vacations: Leaving Norovirus at the Dock. Group B Case Study: CAMRA 3rd QMRA Summer Institute, Michigan State University, East Lansing, MI.
   Accomplishments by S. Devin McLennan

   Tularemia Case Study for 3rd QMRA Summer Institute
   Mendoza-Sanchez, I., F. Simmons, C. O'Donnell, M. Sato, A. Rajić, B. Mayer, A. Jenkins, J. B. Rose, and G. Medema. Tularemia in Water: A Quantitative Microbial Risk Assessment. Group C Case Study: CAMRA 3rd QMRA Summer Institute, Michigan State University, East Lansing, MI.
   Accomplishments by S. Devin McLennan

Avian Influenza Case Study for 3rd QMRA Summer Institute

Gurian, P., I. Young, M. T. Pepe Razzolini, R. Johnson, B. Schmidt, C. Flemming, T. Hong, and A. Smith. Risk Assessment for H5N1 Influenza A: Border Inspection of Smuggled Goods Exposure. Group D Case Study: CAMRA 3rd QMRA Summer Institute, Michigan State University, East Lansing, MI.

Accomplishments by S. Devin McLennan

6. Organization of workshops:
   3rd QMRA Summer Institute, Michigan State University, East Lansing, MI, August 10-15, 2008.
7. Participation in workshops:
   3rd QMRA Summer Institute, Michigan State University, East Lansing, MI, August 10-15, 2008.
8. Case studies:
9. Algorithms developed:
10. Human Resource Development:
11. Funds Leveraged (additional funding. resources for free):

9. Outcomes (how your contributions can be used to better society):
   Unit 156: Combined data analysis of gathered data, increased awareness of remaining research needs for fomite studies, informed design of standard method for fomite sampling
   Unit 346: Professional development, sharing of CAMRA knowledge, completed risk assessments for case studies.
   Unit 347: Student / Professional development, case study risk assessments completed
   Unit 350: Risk assessment for anthrax release, student / professional development
   Unit 352: Quantitative microbial risk assessment for norovirus outbreaks from contaminated houseboats, student / professional development
   Unit 354: quantitative microbial risk assessment for tularemia contamination from infected animal in water distribution system, student / professional development
   Unit 382: Improved and wider use of QMRA, a shift toward quantitative microbiology
   Unit 383: Improved and wider use of QMRA, shift towards quantitative microbiology.

10. Integration with other projects (association between units in different projects): Integration Projects (I-V) draws on all projects to design workshops, educational material, and meetings.

11. Tasks for Next Year: IV (Sep 15 2008 to Sep 14 2009)

12. Anticipated Technical Results and Developments (examples of potential learning units for next year, within possible also include potential outcomes):

Appendix C: Third CAMRA All PI Meeting
October 15-17, 2008
Meeting Summary

Background

The third annual CAMRA All PI meeting was held on October 15-17, 2008 at Arizona State University, Phoenix, Arizona. This report contains the following information pertaining to the meeting and meeting proceedings:

- Meeting Agenda and List of Participants
- Key Ideas from Progress Reports
- Group Discussions and Feedback
- Design Criteria for the CAMRA Data Warehouse
- Observations and recommendations for future project direction and management

This summary was compiled by S. Devin McLennan, Michigan State University

Meeting Agenda

Agenda   Wednesday October 15th
ASU Memorial Union – Mohave Room

Noon – 1:00PM WORKING LUNCH: Welcome and Updates (Joan Rose)

1:00 – 1:30   OVERVIEW
- New Participant Introductions
- Agenda Review and Goals for the Meeting
- CAMRA Updates

1:30 – 5:00   MIDTERM PROJECT PROGRESS REPORTS (All PIs, 10 min each)
- 1:30-2:30 Project I PIs; 2:30-3:00 Break; 3:00-4:30 Projects II, III; IV, PIs; 4:30-5:30 Project V PI
- Major Accomplishments to date
- Year 3 Current Activities
- Remaining Activities – Years 4/5
- Cross-Project Collaboration Needs – Years 4/5

Twin Palms Hotel – Conference Room

5:30 – 7:30   OPEN DISCUSSION (Refreshments)

Agenda   Thursday October 16th
ASU Memorial Union – Mohave Room (Presentations), Gila and Graham Rooms (Discussion)

8:20   Refreshments
8:30 - 9:00AM   CHARGE FOR THE DAY (Joan Rose)

9:00 - 10:00   KEY IDEAS FROM PROGRESS REPORTS (Jan Urban-Lurain)

10:00 - 12:00   PROJECT I TEAM SESSION (Gerba et al.)
                 (Presentation w/small group discussion and feedback)
                 - What are the data gaps?
                 - What organisms should we focus on?
                 - What scenarios should we focus on?

12:00-12:30PM LUNCH Open Discussion

12:30 - 2:30   PROJECT II TEAM SESSION (Eisenburg)
                 (Presentation w/small group discussion and feedback)
                 - What parameters are in the infection models?
                 - How do we reduce the uncertainty of parameters?
                 - What experiments need to be run?

3:00 - 5:00   PROJECT IV TEAM SESSION (Gurian and Casman)
                 (Presentation w/ group discussion and feedback)
                 - How can you use Project IV data and data analysis techniques?
                 - How can risk analysis inform models / experiments?
                 - What organisms / scenarios should we focus on?

5:00 – 6:00   ADMINISTRATOR SESSION (All PIs)

Agenda   Friday October 17th
ASU Memorial Union – Gold Room

8:20 AM   Refreshments

8:30 - 10:00   PROJECT V TEAM SESSION (Weber and Rose)
                 (Presentation w/ group discussion and feedback)
                 - Demo / Introduction to Knowledge Repository, Version 2.
                 - Entering learning units.
                 - Preparing reports.

10:00 – 10:30   THE CAMRA DATA WAREHOUSE (Sid Gunawardena)
                 - What data belongs in the warehouse?
                 - What functions do we want from the warehouse?

10:30 - 10:45   ANNUAL REPORT UPDATE (Devin McLennan)

10:45 - 11:00   SAC FEEDBACK and RECOMMENDATIONS (Stephen Morse)

11:00   MEETING WRAP-UP and ADJOURNMENT

Third All PI Meeting: List of Participants

No	Name	Institution	E-mail Address
1	Joan Rose	Michigan State University	rosejo@msu.edu
2	Syed Hashsham	Michigan State University	hashsham@msu.edu
3	Alok Pandey	Michigan State University	alokkp06@msu.edu
4	Amanda Herzog	Michigan State University	herzoga2@msu.edu
5	Carole Bolin	Michigan State University	bolinc@dcpah.msu.edu
6	Devin McLennan	Michigan State University	mclenn10@msu.edu
7	Charles Haas (by teleconference)	Drexel University	haas@drexel.edu
8	Mark Weir	Drexel University	mw88@drexel.edu
9	Sharon Nappier	Drexel University	spn28@drexel.edu
10	Yin Huang	Drexel University	yh89@drexel.edu
11	Patrick Gurian	Drexel University	pgurian@drexel.edu
12	Tao Hong	Drexel University	hongtao510@gmail.com
13	Jade Mitchell-Blackwood	Drexel University	jade@drexel.edu
14	Rosina Weber	Drexel University	RW37@drexel.edu
15	Sid Gunawardena	Drexel University	sg349@drexel.edu
16	Xuning Tang	Drexel University	xuning.tang@drexel.edu
17	Charles Gerba	University of Arizona	gerba@ag.arizona.edu
18	Ryan Sinclair	University of Arizona	ryans@email.arizona.edu
19	Chris Choi	University of Arizona	cchoi@arizona.edu
20	Pedro Romero	University of Arizona	pedromer@email.arizona.edu
21	Ryan Austin	University of Arizona	rgaustin@email.arizona.edu
22	Sonia Frankem	University of Arizona	slfankem@email.edu
23	David Wagner	Northern Arizona University	dave.wagner@nau.edu
24	David Greenburg	Northern Arizona University	dlg2@nau.edu
25	Joseph Eisenberg	University of Michigan	jnse@umich.edu
26	Sheng Li	University of Michigan	shengli@umich.edu
27	Bryan Mayer	University of Michigan	mayerbry@umich.edu
28	Ian Spicknall	University of Michigan	ispickna@umich.edu
29	Elizabeth Casman	Carnegie Mellon University	casman@andrew.cmu.edu
30	Mark Nicas	University of California, Berkeley	mnicas@berkeley.edu
31	Stephen Morse	SAC / Centers for Disease Control and Prevention	sam1@CDC.GOV
32	Suresh Pillai	SAC / Texas A&M University	spillai@poultry.tamu.edu
33	Jan Urban-Lurain	Spectra Data & Research	janul@aol.com

Key Ideas from Progress Reports

The All PI meeting began with each CAMRA Principal Investigator presenting a summary of their contributions to the project, covering the following four topics.
- Major Accomplishments to Date
- Year 3 Current Activities
- Remaining Activities – Years 4/5
- Cross-Project Collaboration Needs – Years 4/5

Presenters:
Project I. Exposure: Detection, Fate and Transport of Biological Agents of Concern (BAC)
    Charles Gerba, Chris Choi, David Greenberg, Syed Hashsham, Mark Nicas
Project II. Infectious Disease Models for Assessing Microbial Risks for Developing Control Strategies
    Joseph Eisenberg
Project III. Dose-response Modeling and Applications
    Mark Weir, Carole Bolin
Project IV. Assessment-Analysis Interface
    Patrick Gurian, Elizabeth Casman
Project V. Knowledge Management, Learning and Discovery
    Rosina Weber

After each presentation, the PI briefly addressed questions from other CAMRA members, and major issues were summarized and discussed in depth the following morning. Several key issues were identified in this discussion.

CAMRA as a whole
- In the two years remaining, we cannot produce all the data for all organisms of interest.
    o We need to find a consensus on what organisms we will study.
    o How do we prioritize our data needs?
    o What work should focus on Category A, B and C threat agents? What work should focus on select agents? How should we use surrogates?
- We need DHS and EPA feedback to finalize our priorities for Years 4 and 5.
- What principals should guide CAMRA work? Is there a framework for integrating the work of Projects 1 – 5?

Project 1
- The literature has no quantitative data on anthrax decay rates.
- The environmental detection limits for anthrax are poorly characterized and experiments should be run to quantify environmental detection limits.
- The fraction of pathogens that reach different target tissues in a host is unkown.
- The role of biofilms in pathogen movement through water distribution systems is unexplored. Biofilms may effect mass balance, resuspension rates, recovery, and detection.
- When both inhalation and ingestion pathways to infection exist, their relative importance is often unclear.

Projects 2, 3, 4
- Should our research be examining both infection and clinical disease?
- How do we address the risk to sensitive subpopulation?
- Under what conditions can we combine data sets for dose-response?
- How do we address animal-to-human extrapolation for dose-response?
    o Haas Hypothesis: With a competent animal model there is no interspecies variability.
        ▪ Evidence and reasoning needs to be published and debated by the wider scientific community.

- - How do we define a competent animal model?
  - How do we look for competent animal models?
  - How do we validate them?
- What is the practical relevance of non-zero risk targets? Can we measure pathogens at low enough level to determine if a risk target is met?

Opportunities for Further Cross-Project Collaboration
- Project 2 wants to incorporate fomite transfer/survival data from Project 1 into its disease transmission models.
- Project 4 wants Project 1 to measure how long influenza remains viable on fomites.
- Project 4 wants to analyze Chris Choi's water distribution system data from Project 1.
- Project 1 wants to know if/which experiments could help Project 3 with low dose extrapolation for dose-response relationships.

The goals of the upcoming group discussions were redefined to address these key issues from the perspective of each project.

Group Discussions and Feedback

To help establish goals and research needs for Years 4 and 5, Projects I and II conducted breakout sessions and Project IV held a discussion session. Project V presented a workshop on Version 2 of the CAMRA Knowledge Repository and solicited input on the design of the CAMRA Data Warehouse. Key points from the discussions are listed below.

Project I:
- For Years 4 and 5, CAMRA will focus on the model organisms *Bacillus anthracis*, *Francisella tularensis*, and influenza virus.
- The surrogates *Bacillus thuringeinsis*, *Escherichia coli* K12, MS-2 bacteriophage, P22 bacteriophage, vaccine strain influenza, and inactivated Cryptosporidium will be used for surrogate investigations. The comparability between these surrogates and the model organisms will be measured experimentally.
- Hand-to-fomite and fomite-to-hand transfer efficiencies are unknown. Project I will measure these transfer efficiencies directly using CAMRA surrogates.
- Inactivation of microbes on skin is unknown. Project I will measure skin inactivation rates directly using CAMRA surrogates.
- Transport models will be tested with at least 1 virus, 1 protist (for water), 1 spore forming bacterium, and 1 non-spore forming bacterium to encompass the broadest categories of pathogens. These data sets will provide a quantitative approximation for estimating transport of any pathogen in these categories.

Project II:
- In order to access sufficient data for modeling, natural disease must be used as a model for bioterror agents. Project II will focus on influenza and Norovirus modeling to cover the air and fomite transmission pathways for infectious bioterror agents.
- Other projects identified many data sources that will reduce uncertainty in the parameters for Project II's infectious disease models.
- Project I provided suggestions to improve the realism of models regarding transport of pathogens in the environment.
- Project II was tasked to prioritize its model parameters to identify which were important enough to justify direct, experimental measurement. Key parameters were found to be within the scope of Project I's work.

Project IV:
- Project IV will focus decision models on CAMRA model organisms: *Bacillus anthracis*, *Francisella tularensis*, and influenza virus.

- Microbe survival on fomites, microbe recovery from fomites, and interspecies dose-response data sets will be investigated using Baysian Heirarchical Analysis to identify species clusters and meta-distributions for attenuation rate, percent recovery, and dose-response constants.

Design Criteria for the CAMRA Data Warehouse

CAMRA has already gathered and generated a large amount of data on the fate and transport of Biological Agents of Concern (BAC) in the environment and on dose-response relationships for BAC. As part of CAMRA's goal to provide the results of our work as tools for risk analysts, policy makers, and emergency managers, we will be making these and all forthcoming data sets, models, and risk analyses publicly available in an online Data Warehouse. The warehouse should not only present CAMRA information, but also serve as a growing and ongoing nexus for exchanging data and ideas about quantitative microbial risk assessment. Sharing QMRA data on this large scale will help spark collaborations between researchers and advance the field of microbial risk assessment beyond CAMRA Year 5.

With construction of the Data Warehouse about to begin, CAMRA PIs were asked what functions they want from this tool, to ensure that it will meet the needs of its target audience. The following criteria were given.

1. The contents of the data warehouse should be based on sources that CAMRA investigators use for their work. Investegators identified the following as important sources:
   a. Online Articles
   b. Personal Communication
   c. Experiments
   d. Publicly available data from the CDC, USGS, Pubmed, etc.
   e. Industry standards and handbooks
   f. Utilities
   g. Published meta-analysis
2. Files in the data warehouse should use a standard spreadsheet or table format and contain all raw experimental data as well as summaries, statistical analyses, and conclusions. Users should be able to understand exactly what experiment generated the data. Complex data sets should have an attached file demonstrating the calculations used to create each value.
3. All contents of the data warehouse should be freely available to all users. Thus, no private or sensitive information should be put into the warehouse. Criteria should be established to ensure that no sensitive information is put into the data warehouse, but within those criteria all relevant data gathered or generated by CAMRA should be distributed through the data warehouse.
4. Relevant data for the warehouse includes:
   a. Dose-Response parameters and data
   b. Inactivation rates
   c. Parameters for exposure assessment
   d. Water quality models
   e. Published refereed journals and proceedings
   f. Fate and transport models
   g. Decision criteria and analyses
   h. Instructional materials for QMRA
5. Users should be able to freely add data to the Data Warehouse. Quality control standards for additions should be made clear and unsuitable data removed or labelled with a warning, but no user should denied the ability to contribute.
6. All entries in the warehouse should note the original source of the data and provide a way to contact the owner of the data. Published data should include a copy of the research article if freely available, or a link to the publisher if proprietary. Data sets from literature reviews should note all sources used in the review.

7. The warehouse should have a powerful search engine. Search results should be easy to understand.
8. Users should be able to preview the first few lines of any data set before downloading.
9. Users should be able to freely comment about entries, noting how they've used data, posting questions, or requesting revisions to the data set. The ability to add comments will add context to the data sets, help building a sense of community among Data Warehouse users, and allow previous users to aid future users in applying data to risk assessment. A wiki format has been suggested for the comment feature.
10. The warehouse should remain operative and available beyond the end of CAMRA year 5, so that it can grow and serve as a tool for microbial risk assessment. Collaborations supporting other online research tools like *ProMED* outbreak information system and *silva* ribosomal RNA sequence database should be used as models. CAMRA representatives should arrange meetings with the designers of these tools for advice on attracting users and finding financial support for the warehouse.

Observations and recommendations for future project direction and management

CAMRA Administrative Observations

The All-PI Meeting allowed CAMRA researchers to see the progress that each Project had made in three years and to coordinate research for the next two years toward the goal of producing comprehensive and quantitative risk assessments three model organisms. Because CAMRA cannot create comprehensive data sets for all organisms of interest, these model organisms will be used to demonstrate data and model detail sufficient for QMRA.

CAMRA's model organisms will be *Bacillus anthracis*, *Francisella tularensis*, and influenza virus. Much research has already been devoted to *Bacillus anthracis* and *Francisella tularensis*, and Project II's modeling work has focused largely on influenza transmission. CAMRA will devote most of its remaining experimental work to characterizing these organisms for QMRA. Experiments will also test transport models using a representative of each general class of microbes: virus, protest, spore forming bacteria, and non-spore forming bacteria.

Beyond the model organisms. Project II will also focus on Norovirus as a model system for transmission of infectious disease via fomites. Project III has made steady progress producing dose response models and does not need to limit its scope – dose response models for all Category A, B, and C Threat Agents and Select Agents will be completed by Year 5 where suitable data is available. Project IV will focus on CAMRA model organisms and other well characterized biothreat agents, avoiding poorly characterized agents in order to demonstrate the use of complete and quantitative data in risk assessment and risk management. Project V will finish version 2 of the knowledge repository and focus its efforts on building and populating the CAMRA data warehouse to help future researchers build off CAMRA work.

In order to prepare and respond to the threat of deliberate or accidental release of bioterror agents, the movement and health hazard of these agents needs to be characterized quantitatively. QMRA not only shows the size of risk, but also identifies key points for intervention. CAMRA is devoted to providing researchers, risk analysts, policy makers, and regulators with a framework for developing realistic, quantitative microbial risk assessments. Our surrogates, data sets, transport models, and dose response models – gathered in the CAMRA data warehouse – will provide the foundation for future analysis. Our case studies of anthrax, tularemia, and influenza will demonstrate how these factors can be combined to quantify exposure and risk to a degree that even uncertainty is quantified. Creating a strategy to produce these outputs in the next two years has been the key accomplishment of the Year 3 All-PI Meeting.

SAC Observations:

October 23, 2008

Joan B. Rose, Ph.D.
Homer Nowlin Chair in Water Research
Department of Fisheries and Wildlife
Michigan State University
13 Natural Resources
East Lansing, MI 48824

Dear Dr. Rose:

We would like to thank you and your colleagues for their presentations at the recent CAMRA All PI Meeting held October 15-17 in Tempe, Arizona. CAMRA is an ambitious program and the investigators need to be commended for addressing previous SAC recommendations. Specifically, the SAC had felt there was a need for: 1) a mechanism for a stronger integration and coordination of project goals; 2) a clearer definition of key scientific underlying goals; 3) a mechanism for the translation of the science and communication of the outcomes to make a strong impact; 4) greater mentoring and interactions among student colleagues across campuses; and 5) that the quantification of uncertainty should be central to experimental design, and should be considered in CAMRA's research priorities. Overall, we felt that there was very good progress on a number of fronts on the original objectives that were identified by CAMRA. This was substantiated by a number of high quality publications, reports, and presentations made by CAMRA investigators over the past year. Graduate student and post doctoral training is taking place and the quality and enthusiasm of the students and fellows is good. Some of them are already exhibiting strong leadership skills and knowledge as evidenced by their participation at this meeting. It is likely that this level of student and post doctoral training will have a significant impact on the field in the future.

CAMRA has been in existence for about 3 years. Over this time, the focus has become somewhat more diffuse. Dr. Rose has recognized this and is working to identify the priority agents and keep research activities focused and timely. It is tempting to be more expansive, but one should not lose site of the overall goal of the project. CAMRA will not be able to produce all of the data it wants in the next 2 years. In addition to prioritization, it will be necessary to focus activities around several organisms and on key principles.

The Knowledge Management tool is very interesting and novel. It was apparently developed to track progress by articulating outcomes for each project's activities as well as for overall Center activity. It will also be used to identify existing collaborations as well as where collaboration is needed. Based upon the presentation, the tool may be considered by some investigators to be somewhat labor intensive. One concern is whether all of the PIs have bought into this approach of managing information as it will be most useful if everyone participates. Providing all CAMRA investigators with monthly reports on Knowledge Management activities (e.g., entries, searches, etc.) might increase participation.

CAMRA should be more proactive with their sponsors, the Department of Homeland Security (DHS) and the Environmental Protection Agency (EPA). It is recognized that CAMRA is funded through a grant mechanism. However, there are a number of DHS and EPA working groups and projects that could benefit from the involvement of CAMRA investigators. This involvement could enhance the visibility and importance of the work of CAMRA investigators, address gaps in knowledge for DHS and EPA, promote the need for continued funding of CAMRA (its never to early to start thinking about this), and open hiring channels for CAMRA trainees.

In summary, we were extremely pleased with the progress and collaborations fostered through CAMRA. We look forward to working with CAMRA in the future.

Sincerely yours,

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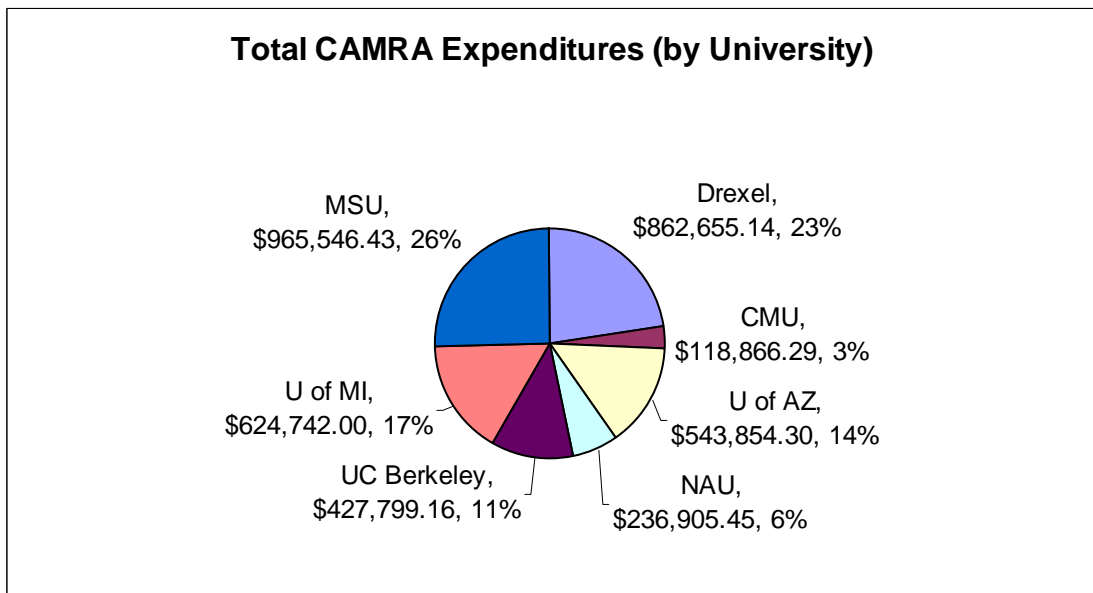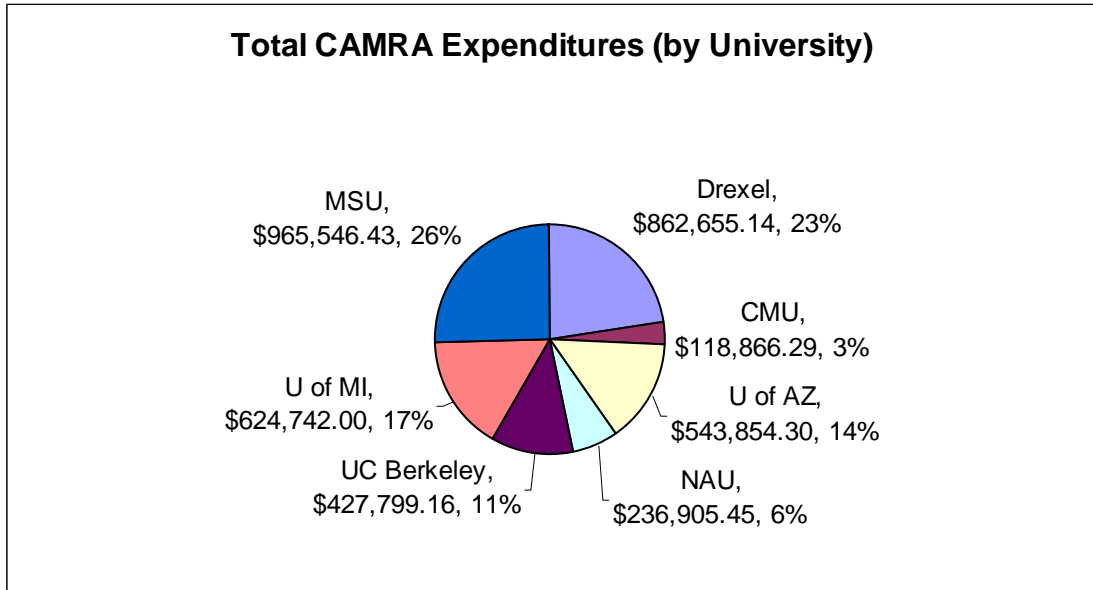**Appendix D: Learning Units – Completed and In-Progress**

Investigators	Status of Year-3 Tasks
Dr. Joan B. Rose Co-Director MSU Integration (Projects I-V) (Postdoctoral) Dr. Yoshifumi Masago Dr. Tomoyuki Shibata (Grad student) S. Devin McLennan	(Completed) • Bacteriophage P22 and Staphylococcus aureus Attenuation on Nonporous Fomites as Determined by Plate Assay and Quantitative PCR: LU 345 • 1-day QMRA Workshop at ASM 2008 General Meeting: LU 383 • 1-week QMRA Summer Institute 2008: LU 347 • Instruction Manual for QMRA 3rd Edition: LU 358 • Anthrax Case Study for QMRA Summer Institute: LU 351 • Norovirus Case Study for QMRA Summer Institute: LU 353 • Tularemia Case Study for QMRA Summer Institute: LU 355 • Avian Influenza Case Study for QMRA Summer Institute: LU 357 (In progress) • CAMRA Fomite Research Matrix: LU 156
Dr. Charles P. Gerba Dr. Ian L. Pepper Univ. of Arizona Project I (Postdoctoral) Dr. Ryan Sinclair Sonia Frankem (Grad student) Jessica Henley	(In progress) • MS-2 Phage and Salt Tracers to Characterize Axial Dispersion: LU 265 • Criteria for Selection of Microbial Surrogates: LU 266 • Survival of viral pathogens on fomites: LU 267
Dr. Chris Choi Univ. of Arizona Project I (Grad student) Ryan Austin Pedro Romero	(Completed) • Water Quality Modelling in Potable Water Distribution Systems: LU 253
Dr. David Wagner Dr. Paul Keim NAU Project I	(Completed) • Validation of a surrogate for *B. anthracis*: liquid short-term: LU 79 (In progress)

(Postdoctoral) Dr. David Greenberg	• Validation of a surogate for B anthracis: liquid long-term: 325 • Validation of a surrogate for *B. anthracis*: fomites: LU 323 • Validation of a surrogate for *B. anthracis*: soil: LU 328 • Inactivation of *B. anthracis* spores: LU 327 • BSL 3 protocols for *B. anthrcais* surrogate selection: LU 329 • Detecting spore survival with qPCR: LU 331
Dr. Syed Hashsham MSU Project I (Postdoctoral) Dr. Alok Pandey (Grad student) Amanda Herzog	(Completed) • Evaluation P22 recovered from fomites using cultivation: LU 116 • Loss due to recovery Vs loss due to decreased infectivity of P22: LU 131 • Environmental detection limit for methods detecting *B. anthracis*: LU 133 • Quantifying risk estimates from IDL and EDL for *B. anthracis*: LU 173 (In progress) • Evaluation *B. thuringiensis* recovered from fomites - cultivation: LU 104 • Genetic characterization of highly touched and untouched fomites: LU 135
Dr. Mark Nicas UC Berkeley Project I (Grad student) Rachel Jones	(Completed) • Relating time to mixing and air turbulence: LU 140 (In progress) • Airborne particle fate and transport in a test chamber: LU 83 • Experiments on droplet spray exposure as a potential infection pathway: LU 142
Dr. Joseph Eisenberg Dr. James Koopman Univ. of Michigan Project II (Postdoctoral) Dr. Nottasorn Plipat (Grad student) Ian Spicknall Sheng Li	(Completed) • Dynamics and control of infections through the environment: LU 372 • The Effect of Exposure Dynamics in Dose Response Relationships: LU 374 • Environmental infection transmission system model for MRA: LU 342 (In progress) • Influenza transmission mode dominance in different contexts : LU 335 • Anthrax Cumulative Dose Response Estimation: LU

Bryan Mayer	336 • Assessment of MRSA transmission in hospital environment: LU 389
Dr. Charles N. Haas Co-Director Drexel Project III (Postdoctoral) Dr. Tim Bartrand Dr. Sharon Nappier (Grad student) Mark Weir Yin Huang Toru Watanabe Sushil Tamrakar	(Completed) • Dose-response model for SARS *coronavirus*: LU 302 • Dose-Response Model for Lassa Virus: LU 316 • Dose-Response Model for *Burkholdria pseudomallei* (Melioidosis): LU 319 • Dose-Response Model for *Coxiella burnetii* (Q fever): LU 321 • Quantifying the Effect of Age on the Dose Response of Smallpox: LU 187 • The effect of Host Species and Aerosol Diameter on risk from Anthrax: LU 283 • Time-dose-response model: LU 298 • Risk-Based Targets for Ambient Monitoring of Pathogens: LU 306 • Equine Encephalitis – Literature Review: LU 218 • A Clinically Relevant model of SARS in mice: LU 297 (In progress) • Dose-response model for influenza A virus: LU 294 • Equine Encephalitis Dose Response: LU 386 • Physiologically Based Pathogen Transport and Kinetics Model : LU 211
Dr. Carole Bolin MSU Project III	(Completed) • Oral Dose Response for three strains of *Francisella tularensis* in mice: LU 215 • Final Oral Dose Response for *Francisella tularensis* in Mice: LU 216
Dr. Patrick Gurian Drexel Project IV (Grad students) Jade Mitchell-Blackwood Tao Hong	(Completed) • Risk-based Targets for Ambient Monitoring of Pathogens: LU 107 • Analytical equations relating aerosol risk to surface concentrations: LU 158 • Bayesian analysis of interspecies dose-response data for *Bacillus anthracis*: LU 160 • Decision model for anthrax treatment and vaccination: LU 162
Dr. Elizabeth Casman Dr. Mitchell Small Carnegie Mellon Project IV	(Completed) • Mental models of influenza transmission: LU 207

Dr. Rosina Weber Drexel Project V (Grad student) Sidath Gunawardena Xuning Tang	(Completed) • Designing CAMRA KR Version 2.0: LU 239 • Designing search for CAMRA KR Version 2.0: LU 59 • CAMRA KR Version 2.0: Designing of Reporting: LU 225 (In progress) • CAMRA KR Version 2.0: Designing of Visualization: LU 222 • CAMRA KR Version 2.0: Testing: LU 226 • CAMRA KR Version 2.0: Implementation: LU 228

Appendix E: CAMRA Expenditures

Total CAMRA Expenditures (by University)

MSU, $965,546.43, 26%

Drexel, $862,655.14, 23%

CMU, $118,866.29, 3%

U of MI, $624,742.00, 17%

U of AZ, $543,854.30, 14%

UC Berkeley, $427,799.16, 11%

NAU, $236,905.45, 6%

Total CAMRA Expenditures (by University)

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CAMRA has been funded a total of $5,820,000 for three years but just recently received year 3 funding in 2008 (originally scheduled to be received at MSU Sept of 2007). Thus as funding was not available some activities slowed down. Some of the PIs continued to spend year 3 funding as their institutions advanced them the monies. Currently the remaining budget for year 3 is $2,028,235 (which is moving into the 4th year of CAMRA operations). The pie charts above provide the allocations of spending to date.

Appendix F: QA Report by Rebecca Ives

QUALITY ASSURANCE REPORT

Center for Advancing Microbial Risk Assessment
Year-3

Submitted by
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Submitted to

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U.S. Environmental Protection Agency (EPA)
Ms. Angela Page
National Center for Environmental Research
U.S. Environmental Protection Agency (EPA)
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Washington, D.C. 20004

And

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

November 26, 2008

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. David Wagner, PI for P1Q5, has taken over for Paul Keim as QAM for that site. Joseph Eisenberg has taken over for James Koopman for as QAM for P2Q6. These changes in personnel are not expected to effect CAMRA's data quality, but has delayed the update of QAPP P2Q6 for year 3. QAPP P1Q4 was delayed due to major revision reflecting that the site had completed all previous experiments and initiated a new one. With the exception of P1Q4 and P2Q6, all final QAPPs were approved by the CAMRA Directors and then reviewed and accepted by the quality assurance officer, Rebecca Ives, by November 2008. QAPP P1Q4 and P2Q6 are undergoing final revisions and corrective action will be taken if completed copies are not submitted in December, 2008.

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	Date QAPP Approved by EPA
I	1	Chuck Gerba	AZ	QAPP P1Q1 Gerba v3_0.doc	02/06/08	03/03/08	**05/29/08**	04/28/08	**06/17/08**		
I	2	Chris Choi	AZ	QAPP P1Q2 Choi v3_0.doc	02/07/08	02/26/08	**03/18/08**	10/06/08			
I	3	Syed Hashsham	MSU	QAPP P1Q3 Hashsham v3_0.doc	02/04/08	x	**07/24/08**	11/03/08			
I	4	Mark Nicas	UCBerkeley	QAPP P1Q4 Nicas v3_0.doc	3/31/2008	05/13/08					
I	5	David Wagner (David Greenberg)	NAU	QAPP P1Q5 Wagner v3_0.doc	02/04/08	02/20/08	**03/21/08**	09/16/08			
II	6	Joe Eisenberg (Joseph Pujol)	UM	QAPP P2Q6 Eisenberg v3_0.doc	02/09/08	03/11/08					
III	7	Chuck Haas	Drexel	QAPP P3Q7 Haas v3_0.doc	01/29/08	02/04/08	**06/17/08**	02/10/08			
III	8	Carole Bolin	MSU	QAPP P3Q8 Bolin v3_0.doc	02/05/08	02/12/08	**02/12/08**	06/17/08	**06/17/08**		
IV	9	Patrick Gurian	Drexel	QAPP P4Q9 Gurian v3_0.doc	02/05/08	03/14/08	**07/16/08**	07/28/08			
IV	10	Liz Casman	CMU	QAPP P4Q10 Casman v3_0.doc	02/04/08	02/12/08	**02/20/08**	02/20/08	**06/17/08**		
V	11	Rosina Weber	Drexel	QAPP P5Q11 Weber v3_0.doc	02/04/08	02/21/08	**03/05/08**	04/28/08	**06/17/08**		

Audits

In 2008, each QAM conducted a technical systems self audit at their site. In addition, the QAO visited Dr. Casman and conducted a technical systems audit. All audited projects received a list of items to address. The quality managers were 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 during the Casman audit.

Project	University	Lead PI	QA manager	2008 Audit dates	QAPP #
I	AZ	Dr. Charles Gerba	Dr. Gerba	11/25/2008	P1Q1
I	AZ	Dr. Chris Choi	Dr. Choi		P1Q2
I	MSU	Dr. Syed Hashsham	Dr. Hashsham		P1Q3
I	UCBerkeley	Dr. Mark Nicas	Dr. Nicas		P1Q4
I	NAU	Dr. David Wagner	Dr. Wagner	11/25/2008	P1Q5
II	UM	Dr. Joe Eisenberg	Dr. Eisenberg		P2Q6
III	Drexel	Dr. Charles N. Haas	Mark Weir		P3Q7
III	MSU	Dr. Carole Bolin	Dr. Bolin		P3Q8
IV	Drexel	Dr. Patrick Gurian	Dr. Gurian	11/28/2008	P4Q9
IV	CMU	Dr. Elizabeth Casman	Dr. Casman	11/18/2008	P4Q10
V	Drexel	Dr. Rosina Weber	Dr. Weber	11/23/2008	P5Q11

Findings from submitted audits
1. Although there have been some delays in some projects, work is progressing according to the schedules described in the QAPPs
2. For project 1 (P1Q2), areas were identified that need to be updated in the respective QAPPs.
3. Project 4 (P4Q9) neglected a minor point on data management, and are now correcting the oversight.

The following section details the quality improvements that projects have been asked to implement.

P1Q1
   The audit indicated that work had deviated from the project plan, but did not include comments detailing the deviation.

   Quality Documentation
   1. Personnel were asked to add comments explaining negative answers on the QA audit to ensure that deviations did not effect data quality.

P1Q2
   The audit identified that some quality control procedures in the QAPP were out of date. QA standards written before experiments began proved unrealistically stringent and were relaxed

to eliminate redundancy and to reflect the actual capabilities of equipment. Personnel have been asked to document changes in an update to the QAPP.

Quality Documentation
1. Personnel were asked to confirm that all SOPs used by the project are available on site.

Quality Objectives
1. Personnel were asked to update quality objective criteria in the QAPP to reflect the flow sensor calibration method currently used.
2. Personnel were asked to update quality objective criteria in the QAPP to note that a mass balance mismatch from 5% to 140% in microbiological data is acceptable, based on comparison to scientific literature.
3. Personnel were asked to update quality objective criteria in the QAPP to reflect that a minimum of 15 data points with 5 additional samples to record the tail of the curve is required for each experiment, rather than a minimum of 30 as currently stated.
4. Personnel were asked to update quality objective criteria in the QAPP to reflect that electronic rather than hardcopy backup is used to preserve large digital data sets.

P1Q3
Audit currently in progress.

P1Q4
Audit currently in progress.

P1Q5
Audit has been completed, QAO review in progress.

P2Q6
Audit currently in progress.

P3Q7
Audit currently in progress.

P3Q8
Audit currently in progress.

P4Q9
The audit identified that some method information was stored in the wrong location.

Documentation and records
1. Personnel were asked to add information collected for model parameters and accompanying references to model methods documentation

<u>P4Q10</u>
<u>A site visit was conducted because there was no site visit for this location in year 2. This project consists of surveys, and both the conduct of surveys and the data handling were found satisfactory and in compliance with the QAPP.</u>

<u>P5Q11</u>
Project 5 relates to CAMRA's data management system, the Knowledge Repository and the CAMRA Data Warehouse. The audit identified that all work was proceeding as described in the QAPP and no corrective actions were required.