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CENTER FOR ADVANCING MICROBIAL RISK ASSESSMENT

ADVANCES IN QMRA

A QUARTERLY NEWSLETTER

INSIDE:

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Editors:
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WELCOME FROM THE CO-DIRECTOR

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

CAMRA was established in September, 2005, to advance quantitative microbial risk assessment (QMRA) data, tools, models and frameworks as well as the understanding and application of QMRA. The two major missions are focused on 1) the technical science and 2) knowledge management and exchange. This is the only Center of Excellence jointly funded by EPA and DHS which is addressing and developing the technical information necessary for quantitative microbial risk assessment (QMRA).

CAMRA has addressed a new QMRA paradigm that includes specific dose-response models and key information on pathogen survival and transmission which allows one to address risk, management options and communication strategies associated with human behavior. CAMRA has provided a "quantitative" yard stick that can be used to judge the level of microbial threats and this has been used to determine that the characterization and management of risk that may be venue and scenario specific. This has helped aid in rapidly addressing emergent problems and environmental monitoring and clean-up after natural disasters or terrorist attacks.

We have been and continue to move forward in advancing exposure assessment and pathogen fate and transport headed by Dr. Charles P. Gerba at the University of Arizona. The work performed by the University of Arizona in the research laboratory of Dr. Christopher Choi has allowed for an advancement to the widely used EPANET and applies a more realistic mixing condition at water distribution pipe joints rather than the 50/50 mixing assumption currently used. This advancement has been adapted to a patch program which can be added to the current EPANET program freely available. The patch is currently under testing and evaluation will be available for distribution in early 2010.

Decision science for microbial risks is an important area which needs the integration of social sciences into the QMRA. At Drexel University Dr. Patrick L. Gurian has been making advancements at the intersection between assessment and analysis which are critical for improved decisions based on new science. Dr. Gurian's lab has produced a set of decision models which describe, based on the risks, which prophylaxis to use and when, for a release of *B. anthracis* spores.

Dr. Elizabeth Casman at Carnegie Mellon University has also developed a mental model which describes how the average person reacts to news of influenza and describes how people react to various interventions. This helps to determine how successful intervention strategies may be used and help to describe what might be the most effective.

Dr. Rosina Weber is continuing to work towards means of disseminating the knowledge to as many interested parties as possible. Dr. Weber is currently adapting our internal knowledge sharing program into one that allows for easy searching of all that CAMRA has learned, discovered and developed.

This newsletter has been developed to keep the QMRA community of scientist and other stakeholders informed and connected as new exciting developments occur as a result of QMRA research. We would like this to be an avenue in the future for communicating quickly some of the sciences of microbial risk assessment. We look forward to the continued work and greater developments within the QMRA world and sharing these advancements with you.

Sincerely,

Dr. Joan B. Rose

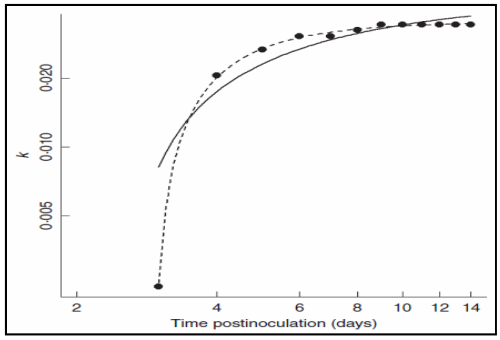

Figure A. Plot showing trend of model parameter

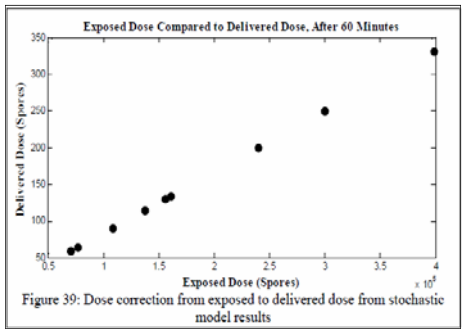

Figure B. Linear factor converting exposed dose to delivered dose

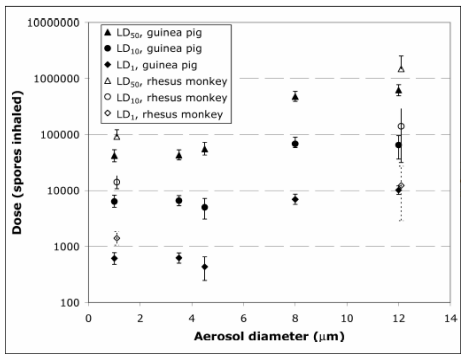

Figure C. Change in LD_{50} from different aerosol diameters

Our advancements are the first of their kind and novel to the microbial risk assessment community.

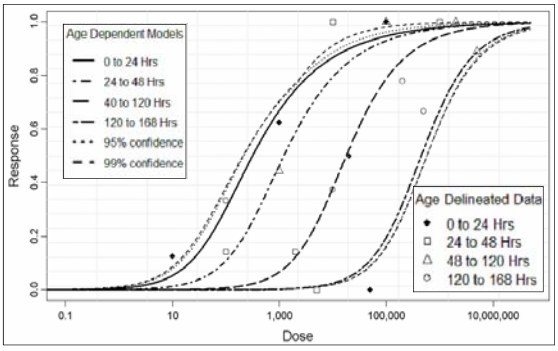

Figure D. Age dependent dose response model for smallpox

ADVANCEMENTS IN DOSE-RESPONSE MODELING

Dr. Charles N. Haas and his group addresses the dose response assessment phase of a QMRA based project at Drexel University. Great strides have been made in building a set of dose-response models and in exploring the science and mathematics of dose response assessments.

For the first time in microbial risk assessment, time post inoculation has been incorporated into two of the classic dose-response models, the beta Poisson and exponential dose-response models.[1] An example of the time dependence of the exponential *k* parameter is shown in Figure A.

This time inclusion is being used to incorporate both time post inoculation as well as multiple dosing. This is key to understanding when the host is exposed to multiple doses over time (eg.10 sets of 10 spores for a total dose of 100 spores) how this may alter the dose-response models and ultimately the health outcomes. Current work focuses on how to include this factor into the commonly used models. This area is an emerging integration of math and biology and represents fertile ground for more work. Thus far these time dependences have been developed for *Bacillus anthracis* (*B. anthracis*), *Frasicella tularensis* and *Yersinia pestis.*

Physiology factors are also important in dose response modeling. Taking into account both transport and kinetics of inhaled *B. anthracis* spores, a correction parameter has been developed (shown in Figure B for transport). This allows for a working framework that addresses physiological dose-response models.

The effect of aerodynamic diameter of *B. anthracis* spores on the dose-response of the inhaled spores has also been determined. This gives an insight into the dynamics of how the dimensions of the spore (just as known for particulate matter) affect the modeled dose-response relationship (Figure C). In addition the combination of data sets has been proposed for *B. anthracis* where it has been shown that there is no need for interspecies extrapolation which will simplify the use of the dose response models for human exposure.[2]

Host age and changes in the dose response model for *Variola major* (*V. major*) has been shown for the first time in microbial risk assessment. Figure D shows the change in the modeled risk base on the inclusion of the age of the host as a factor, and demonstrates the increased susceptibility of the young.[3]

CAMRA has now modeled the basic dose response relationships for all CDC Category A agents, and all available Category B agents (Figure E showing *Burkholderia pseudomallei*).[4] Most of these also have low dose extrapolation.

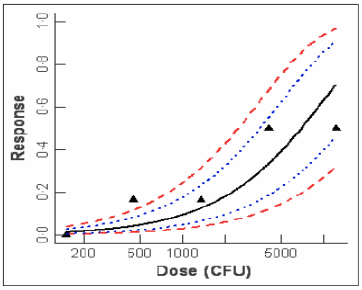

Figure E. Dose response of *Burkholderia pseudomallei*

References
1. Huang Y. *et al* (2009) Applied and Environmental Microbiology 107:727-735
2. Bartrand, T.B. *et al* (2008) Risk Analysis 28(4): 1115-1124
3. Weir, M.H., and Haas, C.N. (2009) Human and Ecological Risk Assessment
4. Tamrakar, S.B. and Haas, C.N. (2009) Journal of Applied Microbiology 105: 1361-1371

ELUCIDATING *BACILLUS ANTHRACIS* ENVIRONMENTAL DETECTION LIMITS

B. anthracis has long been a biological weapon and the bioterror attacks through the postal system in 2001 highlighted the continued use of this particular pathogen.

A problem with both remediation and other post-attack decisions is determining the actual amount of spores used in the attack. This concern opens questions of sampling strategies as well as detection limits for the measurement methods.

For a rapid method there is often a high detection limit thus many spores are needed to show up as a positive for the contamination. The research team of Amanda Herzog and Dr. Syed Hashsham of Michigan State University have worked towards answering what this non-detect might mean in terms of risk by addressing the environmental detection limits (an example of the risks is shown in Table 1 below and detection limits in Figure 1).

By performing an extensive literature survey, backed up by original research the research team at MSU has been able to shed light on the environmental detection limits from a *B. anthracis* release.

Risks ranged from 3 to 7,800 infections per 10,000 at the detection limit dependant on the amount of (time-weighted) exposure.

Looking into a list of rapid methods and how these affect the computation of the risks associated to human exposure with the released spores, this work has allowed very important insights into how the risks and decisions based could be tied better to monitoring of the environment.

Reference
1. Herzog, A.B., *et al* (2009) Applied and Environmental Microbiology **75**(19): 6331-6339

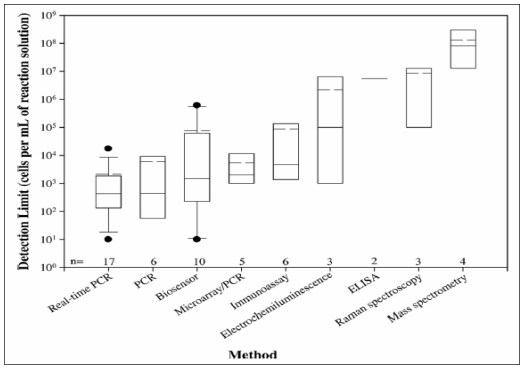

Figure 1. Range of detection limits for various different methods

A mixture of an extensive literature review and original research have allowed for insight into environmental detection limits of *B. anthracis.*

Table 1. Example of risks estimated based on detection limits

			Estimate of Risk for Percent of Sample Inhaled			
Risk Scenario	**Analyzed Detection Limit**	**Percentile**	**100%**	**60%**	**10%**	**1%**
Lower Environmental Limit of Detection in Air	17,000 CFU/m^3	5th	0.026	0.017	0.0026	0.00026
		Median	0.22	0.15	0.025	0.0025
		95th	0.78	0.63	0.14	0.015

ADVANCED TRANSMISSION MODELS: CAN WE MODEL HOW INTERVENTIONS AFFECT THE RISK?

It is known that human intervention in environmental condition can alter disease transmission, however this has not been included in the current transmission models used in the field. This new approach is important for microbial risk assessment.

Research being performed at the University of Michigan is looking into a new paradigm for disease transmission by development of advanced pathogen transmission models.

These models include the dynamics of the environment and dose-response which affect the transmission of the pathogens to either new hosts (for communicable pathogens) or to others who have not yet been exposed to the pathogen.

This is shown in an air scenario, where the risk associated with decontamination decreases the risk level (Figure 1).

This is also shown in Figure 2 for fomite related diseases (eg. surface contamination). This is important for pathogens like *E.coli*, norovirus, Influenza and *Cryptosporidium.*

Reference
1. Li, S., *et al* (2009) American Journal of Epidemiology 170(2): 257-265

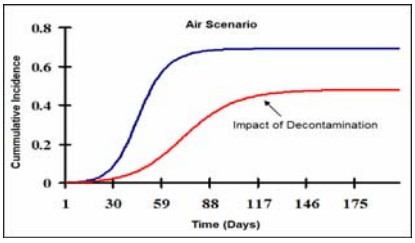

Figure 1. Impact to risks after decontamination in air

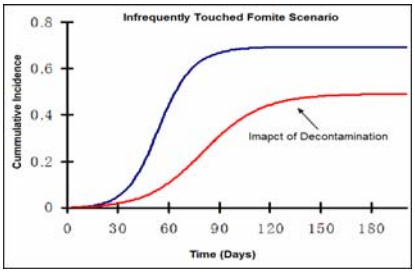

Figure 2. Impact to risks after decontamination of surfaces

CAMRA SUMMER INSTITUTE CASE STUDY TEAM DETERMINE OPTIMAL PREVENTION STRATEGIES

During the 2009 QMRA Summer Institute held at the CAMRA headquarters at Michigan State University a case study based on influenza exposure was analyzed.

One of the main instructional resources of the Summer Institute is the completion of a full QMRA. This intense learning program focuses on integration of data and information into a microbial risk framework to solve specific problems. This year the influenza group produced one of the most outstanding case study results in the four year history of the Summer Institute.

Students benefited from the availability of an advanced transmission model built by CAMRA student researcher Ian Spiknall from the University of Michigan. The transmission model provided the ability to determine how the virus is being transmitted person to person. The model took into account cleaning and decontamination strategies as well as human factors (behavior, etc.) in order to determine the likely transmission levels of the influenza virus.

Using this advanced model the case study group modeled the effect of various realistic intervention strategies, including: hand-washing, wearing a protective mask, surface decontamination and a control situation of doing nothing.

The group took into account the costs of each and determined both the most cost-effective strategy that reduced the risk of transmission the most (number of sick children).

The case study group determined that a combination of surface decontamination and wearing protective masks provided both the greatest risk reduction and most cost-effective approach to protection of children in elementary schools, during an influenza outbreak.

Students benefited from the advanced [influenza] transmission model . . . and determined the most cost-effective options which reduced the risk levels the greatest.

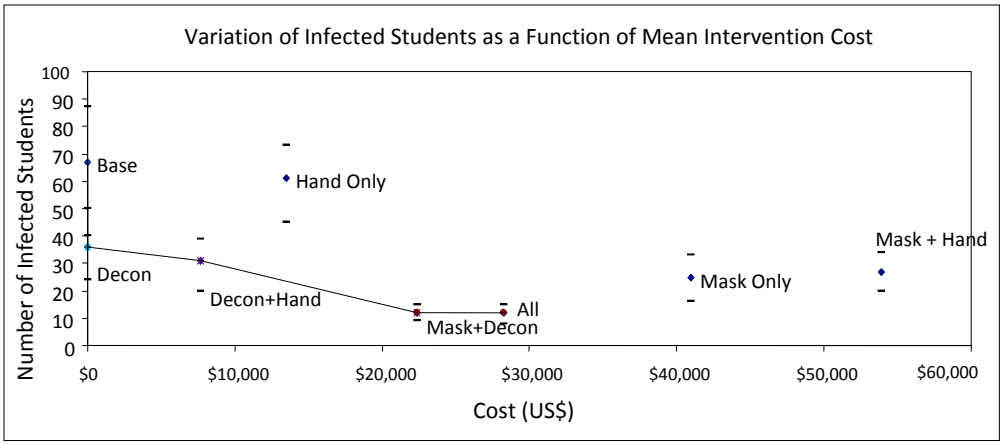

Figure 1. Plot showing variation from intervention strategy, developed by the influenza student group.

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