Technical Evaluation Report

State-of-the-Art in Research on Medical Countermeasures against Biological Agents

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1.0 INTRODUCTION

Several NATO countries have for many years conducted research and development on Medical Countermeasures to Biological Warfare (BW) agents. During the cold war, after the U.S., United Kingdom, Canada, and others had halted their own offensive BW programs, they continued to work with threat agents "…of types and in quantities that [*can be justified*] for prophylactic, protective or other peaceful purposes", in accordance with article I of the Biological Weapons Convention of 1972. Their goals, in most cases, were to develop vaccines, drugs and diagnostic tools to protect their own and NATO forces on a European battlefield during a Soviet offensive. After the fall of the Soviet Union or after their freedom from its domination, other nations have joined NATO and now conduct this important defensive work. Most military medical biological defense laboratories worked quietly during the 1990s, often almost unnoticed by their governments and typically with small budgets. After the Al Qaeda attack of 11 Sep 2001 and the 'anthrax letters' less than a month later, several governments greatly increased their budgets for biodefense, expanding what had been primarily a military medical enterprise to academic and even industrial laboratories in their countries. Some of the larger and more active countries within NATO also increased collaborations. Finally, the new funds injected into these programs, particularly during the first decade of the 21st century, resulted in advancements in our understanding of pathogenesis and bolstered research on and early development of countermeasures against what were traditionally considered *emerging infectious disease*. While traditional threat agents - such as those weaponized during the cold war - are still potential threats, others have been added to various threat lists. It appears that biological threats of today might originate within smaller technical footprints in nation states or as more primitive weapons from non-state actors.

Six to eight months before the subject meeting was held an Ebola virus epidemic began in West Africa, soon engulfing the states of Liberia, Sierra Leone and Guinea with a spillover of individual cases to other African and European nations and the United States. As this three-day meeting progressed there were reports of one or possibly two new diseased health care providers in the United States following their involvement in care of a Liberian American who traveled from his homeland to the state of Texas. It was with this backdrop that the HFM-239 symposium was held in beautiful Vilnius, Lithuania, an historic city then bursting with autumn gold.

2.0 THEME

The NATO Human Factors and Medicine panel's purview is broad, but a necessary diversity and depth is reflected in the makeup of the panel of experts responsible for its implementation. *The mission of the Human Factors and Medicine Panel is to provide the science and technology base for optimizing health, human protection, well-being and performance of the human in operational environments with consideration of affordability. This involves understanding and ensuring the physical, physiological, psychological and*

cognitive compatibility among military personnel, technological systems, missions, and environments. This is accomplished by exchange of information, collaborative experiments and shared field trials. A panel meeting focused, as this one, on a narrow theme cannot occur often. Whether by chance, great wisdom of foresight---planning was begun years in advance---or because 'it just hadn't been done for a long time' the theme of medical countermeasures to biological agents couldn't have been timelier. None-the-less, it is unlikely to have occurred at all were it not for members on the panel who understood the importance of the subject matter and the dedication of scientists and clinicians across our laboratories who have been working quietly for years, first to deal with what we believed were 'known' and more recently the 'unknown' threats and risks.

3.0 PURPOSE AND SCOPE OF MEETING

The meeting was planned and held to bring together experts from NATO nations to review progress, share and compare thoughts and underscore the importance of medical countermeasures for biological defense. While there are clearly medical information- and materiel requirements unique to protecting our military forces and our citizens from biological weapons, these have similarities to what are needed to deal with emerging infections and even, what could well be our 'next pandemic': antimicrobial resistance. The focus of this meeting was on vaccines, diagnostic tools and antiviral and antibacterial therapies but the planning committee included critical but more subtle and less often highlighted activities such as animal model development, pathogenesis research, threat analysis, regulatory approaches to countermeasures development and even examples of cross-ministry domestic- and international collaboration.

The 'problem' of BW is often parsed into "prevention, preparation, response and recovery" or into "medical and non-medical" preparation. Components of biodefense and response are often examined through the lens of chemical or even nuclear weapons threats. Furthermore, the three---or four (the fourth being radiological) potential weapons systems are often lumped into a category called Weapons of Mass Destruction (WMD) and have often been ignored by traditional military planners because their use is considered unlikely or the impact of it on military forces is just too complex and daunting to plan for or 'game' in training. By teasing out a defined subset of the most relevant issues and addressing them systematically, with adequate depth and in a nicely coordinated fashion, the planning committee was able to clearly illustrate the state-of-art and potential gaps in this important field of medical countermeasures preparation and security doctrine.

4.0 EVALUATION

The organizing committee is to be commended for planning a balanced content and an appropriate level of complexity for the intended audience. Dr. David Christopher (Chris) Hassel, Deputy Assistant Secretary of Defense (DASD) for Chemical and Biological Weapons from the U.S. Department of Defense, provided the keynote. The address (not included among the manuscripts) provided an excellent introduction to the topic and the meeting. First the DASD addressed the spectrum of risk which includes naturally occurring infectious disease, accidental laboratory exposure, conduct of legitimate research that is subsequently used for harm (often called "Dual-Use Research of Concern"), insider misuse of biology, bioterrorism and even state sponsored BW. He addressed the often-misunderstood differences between "chem" and "bio" threats and talked about "internal" and "external" countermeasures (sometimes called "medical" and "non-medical"). He then described the U.S. government approach to these challenges as "whole of government", explaining briefly how the various departments have come to work together, particularly after the attacks of 2001. Dr. Hassel described the concept of "Interim Fielding Capabilities" a broad series of approaches the U.S. government is taking to make safe but unlicensed products available to health care providers in a crisis. Approval of these measures is the responsibility of the U.S. Food and Drug Administration, among them the well-known Emergency Use Authorization (EUA). Dr. Hassel undertook a brief discussion of the Obama administration's recent introduction of the Global Health Security Agenda, which seeks to bring 30 or more

nations together around public health and biosecurity. Finally, he closed with a brief description of U.S. Department of Defense biodefense strategy. It includes four pillars: Reduce Incentive, Increase Barriers, [Deal with] Failed States and Deny Effects.

4.1 Risk Assessment and Regulatory Challenges to Medical Countermeasures

The first paper of the symposium introduced 12 'weapons attributes' used to score agents in an attempt to find a means of prioritizing agent specific preparations for an attack. The authors used a survey tool, querying experienced BW and terrorism defense experts about 33 classical (the 'dirty dozen'), common public health or emerging agents. Results were surprising. For example, ricin toxin was rated #1 threat, botulinum toxin #10 and *Bacillus anthracis,* generally thought by experts to be 'the king of BW agents #21. This attempt to understand the BW or terrorism threat through 'ranking agents' demonstrated again how difficult it is to evaluate the likelihood and impact of a threat based on agent characteristics. These findings support the proposition that the best insurance against a mostly unknowable threat---beyond specific preparation for a handful of agents---is a cadre of human subject matter experts networked domestically in each of our countries and globally, to help us respond appropriately when one of the myriad agents is used against our forces or our citizens. This difficulty of understanding specific threats would inform our thinking about the rest of the papers presented at the meeting.

The regulatory challenges faced by scientists and clinicians attempting to provide medical countermeasures are sometimes also seen as 'threats'; in this case threats to *progress*. The second paper quickly clarified regulatory challenges such as developing product profiles, conducting animal studies, selecting human dose based on animal data, manufacturing issues including conditions of licensure and *Concept of Use* in a military or civilian setting. The importance of working with regulatory authorities early and often became abundantly clear.

4.2 Vaccines

Vaccines, the focus of countermeasure development during the cold war were discussed in the next six papers. Five of the papers described recombinant vaccines developed over the past 20 years by exploiting DNA technologies as they became available. The first paper built on the last in the previous session by using the recombinant plague vaccine construct expressing two antigens (F1 and V) as a fusion protein to illustrate the complexity of applying the 'two animal rule' and the value and difficulty of immunological studies needed to license a biodefense vaccine.

Continuing the theme of transitioning candidate vaccines to advanced development the second paper in the vaccine series described human phase one and phase two clinical trials and, again, the use of an animal model surrogate for efficacy including passive serum transfer from immunized human subjects to guinea pigs before challenge. In this way, the safety of the candidate in humans could be approximated and the best possible estimate of efficacy in humans obtained.

The third paper described a study of the importance of 'schedule' in the use of vaccines for a military force. The legacy product, Anthrax Vaccine Adsorbed (AVA), was given to volunteer service members who had not maintained their booster doses. Up to seven years after the last boost, a single immunization resulted in an antibody response that was "noninferior" in response to a booster given on schedule. These findings suggest it is not necessary to restart an interrupted schedule with this vaccine. The data also suggest that it might be possible to begin an initial series during basic training, early in a soldiers' career and then boost, with good effect, just before deployment a number of years later.

The fourth paper described the research, development and human phase 1 safety trials of a recombinant ricin toxin vaccine. This study illustrated the variation among human subjects. At the highest dose, two genetically related test subjects experienced an adverse reaction. While there were complicating

circumstances unrelated to the vaccine and the adverse events could not be directly attributed to the vaccine, the subjects were removed from the study and the highest dose arm of the trail was suspended. This paper illustrated yet another aspect of the long journey to licensure and the fact that each of the threat agents must be considered individually when developing vaccines; "one size" does not fit all.

The fifth paper illustrated a different technological approach for providing vaccine protection in service members or civilians. Rather than injecting an antigen (a non-pathogenic simulant of a pathogen which causes the immune system to produce a protective response) the DNA coding for the antigen is introduced and the body's machinery produces the antigen and then responds to it. In this particular case, protection was achieved against three related viruses in animal models. Human trials are underway. There have been no safety issues at this point; immunogenicity trial results are pending.

The final paper in this section highlighted yet another recombinant technology for vaccination. In this case part of an actual threat agent virus (Venezuelan Equine Encephalomyelitis virus) was used as a Trojan horse to deliver antigens that produce a protective immune response to filoviruses Marburg and Ebola. The Trojan horse virus is designed to replicate only once after being injected and, by its nature, delivers the payload directly to the cells that are responsible for processing the payload. One of the concerns was that a host might develop immunity to the 'horse' thus it would not be able to deliver another *different* payload at a later date; these data suggest that this is likely not the case. Laboratory animals could be immunized against two viruses concurrently or sequentially and did develop a protective immunity.

While vaccines were the cornerstone of medical biological defense during the cold war because they must be given weeks or months before exposure to a pathogen their lead role may be taken over by therapies----antiviral and antibacterial drugs---in the future. Efforts to produce such countermeasures were addressed later in the course of the conference.

4.3 Diagnostics

Diagnostics have been an important part of medical biological defense kit for many years, but have gained relative importance in the 90s with the biotechnology revolution and the new opportunities it delivered. After the cold war, as our view of the threat became clouded and more diffuse, the case for diagnostics was bolstered further. Then, with an increasing incidence of emerging and reemerging infectious diseases from nature and humans pushing medical care ever further into remote regions, portable and point-of-care diagnostic tools have become sought after.

The opening paper in this session provided a clear and concise overview of what technologies are now available, what is possible today and what we might expect in the future with regard to molecular diagnostics, including next-generation sequencing. We've made good progress. While regulatory compliance of diagnostics is required, as it is for vaccines and therapeutics, the opportunities for pre-licensure testing on real human patients and even the conduct of epidemiological studies using candidate assays does exist. When used by a health care provider to make decisions regarding care of an individual patient, the tests of course must meet regulatory compliance. Examples exist in the context of the current Ebola epidemic in which an Ebola diagnostic was taken just short of licensure long before the outbreak and then approved by the U.S. FDA very quickly in this time of need. The paper also discussed a role for diagnostic tools in pathogenesis studies conducted using animal models.

Paper number two addressed the important concept of Civilian-Military Cooperation (CIMIC) in developing systems for diagnostics and field detection of both public health and BW/terrorism agents and related disease. Working together, at the laboratory level, across agencies within the Romanian government, teams have torn down agency 'stovepipes' and developed systems, protocols and means of information sharing. They developed and tested the best collaborative approaches from multi-species field sample collection to serological, molecular and proteomic methods of analysis. Too often we focus on the technologies and

ignore building the important communities of trust. This group of scientists and clinicians is to be commended for working from the ground-up to develop human relationships that have supercharged technology applications.

Appropriately, the final paper in this session demonstrated an attempt to 'push the envelope'. The authors are evaluating the possibility of exploiting unique natural enzymes (proteases) found in specific pathogens of diagnostic interest by developing amino acid synthetic substrates and utilizing Fluorescence Resonance Energy Transfer (FRET) to follow the reactions. While it is too early to know what potential operational diagnostic or detection systems may result, this work is an example of the kind of very fundamental science that has often lead to breakthroughs in the past.

4.4 Bacterial Therapeutics and Multi-drug Resistance

Since the dawn of the antibacterial age at the end of WW II the pharmaceutical industry has exploited every known natural bacterial vulnerability for drug development. Yet, therapies for viruses eluded us for years. Now, as we are seeing breakthroughs in anti-viral research and development, the bacteria are exploiting weaknesses in our antibacterials…sometimes with human assistance because of inappropriate drug-use behaviors. These realities, along with today's unpredictability of specific intentional threats, have significantly increased the value proposition regarding antimicrobials in general for our medical countermeasures portfolio. This session focused on anti*bacterial* resistance and novel approaches to dealing with it.

The first paper addressed the possibility of using peptides as a new class of compounds against multi-drug resistant bacteria. Anti-microbial peptides (AMP) are part of the innate immune system and have activities against many classes of microbes. Here, lactoferrin, a component of the immune system was used to derive AMPs for testing against well-known threat agent bacteria. Selected lactoferrin AMPs were expressed as fusion proteins then tested and found to be active against certain species. The authors have also demonstrated modes of action of subject peptides. While preliminary results are promising, work remains in operationalizing the idea. Possible advantages of such materials and barriers to success were discussed.

It their drive to develop medical countermeasures, it's easy for bureaucracies to forget the importance of understanding very basic pathogenic mechanisms. We now have the molecular tools to do that more effectively than ever before. The authors of the second paper in this series addressed the molecular and functional basis for antibacterial resistance in *Francisella tularensis* strain Schu4. Not only did they discover altered *in vitro* growth characteristics and nutrient requirements in the resistant strain, but noted that it had lost virulence while retaining immunogenicity. The implications for vaccine development [no good vaccine exists for *F. tularensis*] were discussed.

Continuing the theme of antibacterial resistance, the third paper addressed the bacterial membrane as a barrier to antimicrobial success. Some bacteria are resistant because they have either developed means of 'keeping' the antibiotic out initially or 'pumping' it out once it gets inside the membrane. The research described is seeking to find chemical 'helpers' to accompany antibacterials, assisting to get them in and keep them inside the bacterial envelope. The authors are working with a consortium in the European Union called New Drugs for Bad Bugs, focusing on numerous approaches to overcoming antimicrobial resistance.

The final paper in this section on antibacterials has it roots in vaccine development. In the process of looking at the polyglutamic acid capsule of Bacillus anthracis as both a virulence factor and potential antigen to supplement recombinant Protective Antigen traditionally used in anthrax vaccines, the authors found from in vitro studies that removing the capsule with capsule-depolymerizing enzyme (CapD) rendered the bacteria susceptible to phagocytic killing. Initial studies suggest that this approach might have application in vivo and could possibly be used to treat infections in multidrug-resistant strains.

4.5 Antiviral and Anti-Toxin Therapeutics

While we are currently struggling to develop new anti-bacterial therapies, we have entered the age of anti-virals and *safer* anti-toxins. We have long used polyclonal homologous or heterologous antisera to treat toxin poisoning; now, very specific 'human' monoclonal antibody cocktails can and are begin developed. Likewise the biotech revolution has given us new tools for use against viral disease threats. This session provided some examples of what's possible in the lab today and closed with timely thoughts on improving our care of filovirus patients in the clinic.

The first paper described the development of human-like monoclonal antibodies (Mabs) for use as therapy in botulinum intoxication and Venezuelan and Western Encephalitis virus infections. The authors provided a review of the technology and opportunities for using convalescent lymphocytes from humans or non-human primates, by phage display selection. European or North American regulatory bodies have already approved tens of Mabs or Mab cocktails and hundreds are under development. Most are for cancer or autoimmune disease, but there now two for biodefense indications. They have been proven effective for several applications. At this time, a major drawback to Mab use is cost. As the cost comes down recombinant Mabs and Mab cocktails will likely become a more important part of our biodefense armamentarium.

The second paper reported on the development of human and murine antibodies against ricin toxin and Venezuelan Encephalitis Virus disease. This group of researchers has used two transgenic approaches; the first the well-known tobacco production system and the second a less well known transfection of genes coding for human Mabs via mesenchymal stromal cells (MSC) from human umbilical cord perivascular cells. The MSC approach may skirt the potential problem of an individual having immunity to an adenoviral vector, often used to introduce genes. Also the MSCs have been shown to persist in the body for months, potentially providing relatively long-term protection. Were this system to prove successful, it might result in significantly reduced cost for Mab therapies…or even for prophylactic applications. During the presentation the author raised a provocative question; "Do we really need to humanize these antibodies against biological warfare threats and very rare diseases for which it is very likely that a patient will only be treated once?" This is an example of the kind of "ConOps" thinking that we often do too little of.

The third paper in the set, again extremely timely, described the development of therapeutic antibodies for Marburg virus, a cousin to the now well-known Ebola virus. In this study, non-human primates were immunized with Marburg viral like particles and a library of single chain variable fragments was generated. Some of these antibodies proved therapeutic in a mouse Marburg model when given one day before exposure, and one and three days after. This may be the first report of successful Mab protection in an animal model of Marburg virus disease. As positive as this good technical outcome, the project has the additional virtue of being accomplished through a true partnership between scientists in France, Germany and the U.S. The value of such collaborations goes far beyond just the scientific, by building powerful and potentially long-lasting networks of communication and even trust.

The theme of the final paper in the set was clinical, summarizing previous practices, observations and thoughts on structuring future data collection regarding efficacy of supportive care for filovirus disease management. Because most historical filovirus outbreaks have occurred in low-resource regions, there are limited data on what works and what doesn't. For the most part, there is little reason to believe that symptomatic support of organ systems is *not* a good thing, but only a very few clinicians treating Ebola or Marburg virus patients have had access to state-of-art intensive care resources. Even the few patients transferred to Level 3 medical centers from the current West African Ebola outbreak will likely not provide a very robust data set or statistical significance. The authors propose some specific measures which might prepare us to collect more valuable data during the next outbreak and also suggest some controlled studies in instrumented non-human primates that might shed light on the way ahead for providing supportive care to humans when the need arises.

4.6 Animal Models

For most biological threat agents, the incidence of disease in humans---particularly after exposure by the inhalational route---is low and the cases sporadic, often occurring in remote or under-resourced areas. Therefore animal models have long been used to test efficacy of medical countermeasures. Animals have also been used to study the gross mechanisms and sequence of pathologic events---pathogenesis---and now, with the new tools available, the molecular pathogenesis as well. The three papers in this section addressed animal models for *Brucella* and *Burkholderia* species. While these bacterial species were studied as weapons agents and *Brucella suis* was weaponized by the U.S. offensive program during the 1960s, models of the disease states caused by these agents were not a high priority in the medical defensive programs that followed in the 70s, 80s and 90s.

The first paper described an instrumented rhesus macaque model of brucellosis caused by infection with *B. melitensis* for the study of antibacterial efficacy. Animals were exposed by aerosol challenge and treated with the antibiotic doxycycline or sham therapy for 14 days beginning on day 21 post challenge. Clinical chemistries, cultures, immunological measures and core temperature were collected prior to challenge and through the end of the study. The disease course and post-mortem pathologic change proved to be very similar to the disease in humans. The study not only shed important light on the pathogenesis of disease following inhalational exposure but also improved our understanding of antibiotic therapeutic protocols and has resulted in a viable model for future medical countermeasures studies.

The second paper in this series described the development of animal models of *Burkholderia mallei* (causative agent of glanders) and *Burkholderia pseudomallei* (causative agent of melioidosis). No vaccine candidate for either of these species provides sterile immunity and antibiotic therapy is not always successful; therefore, it is important to develop appropriate models in which pathogenesis can be studied and countermeasures tested. Eleven strains of *B. pseudomallei* were characterized in a mouse model and one strain of *B. mallei* was tested in three non-human primate species (Cynomolgus, Rhesus and African Green monkeys). The African Green Monkey model was the only primate model that demonstrated signs of disease very similar to those seen in humans. These studies have advanced our understanding of two rare diseases and established models that can now be used for the development of medical countermeasures.

The final paper in this section described the development and characterization of two strains of *B. pseudomallei* (etiologic agent of melioidosis) in instrumented animal models using rhesus macaques. After determining the median inhaled lethal dose at 21 days, animals were challenged and followed for bacteremia, tissue burden of pathogen, core temperature and ultimately post-mortem histopathology studies were done. The natural history of the disease caused by the selected test strains in the models faithfully reproduced that seen in human melioidosis. Therefore, this work can also provide a foundation for medical countermeasures evaluation.

It may appear strange to the reader of these reports that this apparently basic work is still ongoing and important in the second decade of the 21st century. Some of the molecular work conducted here could not have been done 20 or 30 years ago, but it is this reviewer's opinion that some of what could have been done was not done because senior level managers in military departments in the past 10-20 years were so focused on 'product development and acquisition' that the science labs were poorly funded to conduct this basic research. It is likely that we will find in the end that the shortest way to a fielded medical countermeasure is through early and robust support of these critical, but often underappreciated, fundamental pathogenesis studies.

4.7 Pathogenesis

As introduced above, much of the very basic work to understand mechanisms of action of threat agents often leads to breakthroughs that ultimately shorten the time to fielding products. It is this reviewer's opinion that

studies of *how the threat organism causes illness* or death and how the *host* responds are absolutely central to making progress in this effort to protect our forces and our citizens. Appropriately, the final session of this excellent meeting focused on the most fundamental: *pathogenesis studies*.

The twin arginine translocation (Tat) system/pathway is one of the methods that *Yersinia pestis*, etiologic agent of the disease called plague, uses to move proteins across membranes and out of the bacterial cell. The first paper in this final session described work to understand the role of Tat proteins in the scheme *Y. pestis* uses to cause disease. In doing this very basic work which required the use of molecular tools and animals models the authors discovered that, without the Tat system, mutant *Y. pestis* was attenuated when given by injection or inhaled aerosol but surprisingly less attenuated when delivered intranasally. The study helped clarify bacterial mechanisms of disease, suggested additional yet-unstudied factors that may be involved and demonstrated potential opportunities to target the Tat pathway in developing medical countermeasures for plague and other bacterial infections.

The second paper in the set addressed the interaction between *B. pseudomallei* (etiologic agent of melioidosis) and a mouse derived macrophage cell line (RAW264.7) by proteomics analysis. The goal was to describe a population of bacterial proteins excreted inside the macrophages---modeling what might occur in the intact animal or human---and attempt to understand the host (macrophage) response to these proteins. The hypothesis is that the proteins produced by the bacteria inside the macrophage will modulate the production of cytokines, chemokines and other host factors that directly drive disease manifestations. Understanding these factors may allow us to target them for medical countermeasure development.

The final paper described work to understand how a toxin produced by the bacteria *Legionella pneumophilia*---not a traditional BW agent, but one important to public health as the etiologic agent of Legionnaire's disease---might impact the central nervous system of patients. It is known that Legionella pneumonia can cause altered mental states. The author studied the effect of bacterial extracts, apparently containing protein-like material, and demonstrated that they caused cell death in monocytes and astrocytes *in vitro*. The resulting hypothesis that will need to be tested *in vivo* is that these yet-uncharacterized factors might be transported from the site of active infection in the lung to the brain and be causative in the disorientation noted.

5.0 CONCLUSIONS

The symposium set out to allow us to share our work and thoughts on medical countermeasures to BW agents. We have traditionally thought of medical countermeasures as finished products---vaccines or drugs ready for administration and analytical tools in an aid station or field hospital for making definitive diagnoses or triaging patients. While licensed products are the goal, we know that, between the science and the regulatory hurdles, putting products on the shelf often takes decades. We discussed every stage of the process from threat to early hypothesis formulation through an example of a licensed vaccine used regularly in humans. In the process, two important lessons for the future became clear: 1) today's threats are far different and far less knowable than those we faced during the cold war---and now include multiple-drug resistant bacteria---therefore 2) a global network of *connected* subject matter experts who have great depth of understanding of the molecular characteristics of a broad range of threat agents and host responses to them…and who are gaining experience and knowledge while *working toward* licensed countermeasures are enormously valuable in today's threat environment. Our laser focus on vaccines was appropriate for the cold war threat, but we must broaden our aperture today. New technical tools and molecular understanding will allow us to produce the diagnostics that we need. In addition, anti-viral, and particularly new anti-bacterial therapies should be a major component of our research and development portfolio. Overall the symposium was very well organized, administratively and technically, and was nicely executed. Involving more young people in the program in the future would help insure long-term sustainability of these good efforts.

6.0 RECOMMENDATIONS

- Think carefully about today's (post-cold-war) threat: it has changed significantly.
- It's not too early to add multiple-drug resistant bacteria to the list of important 'threats'.
- Think about concepts of use for medical countermeasures early in the process.
- Value fundamental research on potential threat agents and on the host response to them.
- Value deep, globally connected Subject Matter Experts.
- Value, mentor and include our best young scientists
- Value and seek international collaborations
- Help educate our political leaders, media and citizens when you have the chance.
- Work together; it's powerful!