



TATRC

Telemedicine & Advanced Technology Research Center

Proceedings from
The Consensus Conference
on the Role of Biosensors in the Detection
of Agents of Bioterrorism

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INTRODUCTION

On 8-9 September, 2003, the U.S. Army Medical Research and Materiel Command's Telemedicine and Advanced Technology Research Center (USAMRMC-TATRC) convened a consensus conference at the Morningside Inn in Frederick, MD to discuss the role of biosensors in the detection of biowarfare agents. The purpose of this conference was to draft guidelines for directing research efforts and to assist decision-makers establish funding priorities in biodefense, as it is currently unclear under what circumstances various technologies would decrease disease morbidity and mortality without incurring prohibitive costs. Impetus for the meeting was precipitated by unresolved issues raised at a biodetector workshop hosted by the National Defense University in December, 2002.

Invited participants were assembled into working groups to discuss 1) threat assessment; 2) public health requirements; 3) technological requirements; and 4) standardization of critical reagents. A planning committee drafted questions and issues for each working group to address. These guidelines for discussion were distributed prior to the conference, to allow time for the designated chairs and group members to prepare in advance of the meeting.

The conference facilitated collaboration among multiple different Government agencies and civilian institutions. Among those participating were representatives from the Department of Health and Human Services, Department of Homeland Security, Centers for Disease Control and Prevention, Joint Program Executive Office for Chemical and Biological Defense, US Army Soldier and Biological Chemical Command, National Institute of Allergy and Infectious Diseases, Office of the Deputy Assistant to the Secretary of Defense for Chemical Biological Defense, State Department, US Army Medical Research Institute of Infectious Diseases, Naval Medical Research Center, Food and Drug Administration, United States Department of Agriculture, Environmental Protection Agency, Armed Forces Institute of Pathology, Canadian CBRN Research and Technology Initiative, The Washington Institute, Fire Department New York, Massachusetts General Hospital, Georgetown University, Virginia Polytechnic Institute and State University, University of Texas, University of Maryland, Drexel University, Auburn University, University of Hawaii, Draper Laboratories, Lawrence Livermore National Laboratory, and Los Alamos National Laboratory (see appendix for full list of participants).

Below is a synopsis of the issues addressed, discussion summary, and summary statements and recommendations for each of the 4 working groups.

Planning Committee

- * LTC Mary Parker, MD, Senior Clinical Advisor, USAMRMC-TATRC, Ft Detrick, MD
- * Peter Emanuel, PhD, Joint Program Executive Office for Chemical and Biological Defense, Critical Reagent Program Director, US Army Edgewood Chemical Biological Center, Aberdeen Proving Ground, MD
- * Jim Wilson, MD, Head, Division of Integrated Biodefense, ISIS Center, Georgetown University Medical Center, Washington, DC and Technical Advisor, Biodefense, USAMRMC-TATRC, Ft Detrick, MD
- * Anne Harrington, Deputy Director, Office of Proliferation Threat Reduction, State Department, Washington, DC
- * Joseph Corriveau, PhD, Deputy Director, Research and Technology Directorate, US Army Soldier and Biological Chemical Command, Aberdeen Proving Ground, MD

Chair

Michael Callahan, MD, MSPH, DTM&H (UK), Division of Infectious Diseases, Program on Biothreat Detection, Center for Integration of Medicine and Innovative Technology (CIMIT), Massachusetts General Hospital, Boston, MA

Issues Addressed by the Working Group

- * *Review constructs and concepts related to threat analysis*
- * *Discuss classification of high risk biothreat agents*
- * *Discuss the concept and potential value of integrated biosurveillance*

Discussion Summary

Evidence-based data from recent mass-casualty incidents (WTC 9/11 and OC 4/95) and catastrophic infections (SARS-Hong Kong and Toronto, FMD-UK, US Anthrax) served as a background for discussion. Although complete reviews of characterized biological weapons could not be reviewed under the unclassified conditions of the conference, members could exploit experiences with naturally occurring disease and OSINT databases and the field experience of participants. The Canadian experience with SARS was felt to be particularly illustrative, as Toronto was considered to be “world class” in terms of its public health response, interagency coordination, and forward thinking viewpoint about potential threats to agriculture and public health.

The working group thought that much of the information relevant to predicting threats and differentiating theoretical inbound threats from naturally occurring disease was based on familiarity with current biological probabilities as well as input from the intelligence community. Determining what types of information were credible was considered key to threat assessment. Group members underscored the importance that the probability that a terrorist group could achieve a biowarfare capability was dictated primarily by the limitations of scientific knowledge and willingness to redirect or convene requisite technologies rather than the difficulties of obtaining a weapons-capable pathogen (exception: smallpox). Group members suggested that stated challenges to acquisition of dangerous agents, technologies, and dispersal methodologies were dangerously overstated. The group emphasized that if threat assessments performed a few years ago were revisited with regard to emerging pathogens, highly efficient, automated and portable technologies and improved laboratory methods, a different and expanded determination of vulnerability would be proposed. It was noted that many new-generation and non-traditional production methods do not have diagnostic and therapeutic countermeasures. The recommendation was made that threat assessments need to be systematically revised with respect to new publications in the medical, biological and technical literature. Specific examples were provided where observations in the “grey” literature influenced the probability and the nature of contemporary biowarfare-relevant production methods.

Phases of the biological threat timeline were defined as pre-event, peri-event, post-event and recovery. Awareness that an event was a possibility defined the pre-event period. Peri-event was the time period surrounding the dispersal of an agent and the early recognition of an infectious disease outbreak. The post-event time period was that immediately following the dispersal or outbreak, and was followed by the recovery phase.

Threat analysis was discussed within two contexts. The group initially reviewed threats relative to populations or time.

It was thought that scientists often focused on the organisms and toxins they were most familiar with. Temporal threat analysis could be conceptualized as retrograde, evaluating an event after it has occurred, or antegrade, a strategic epidemiologic approach to anticipate or predict an event based on tracking of indications and warnings.

Another construct discussed was threat analysis via target identification. This approach involved using reverse engineering to analyze threats to the 8 components of the critical infrastructure listed by the US government: energy, telecommunication, water supply, healthcare, financial services, transportation, manufacturing and food production. Some US government organizations were using a target system developed by the military known as CARVES, which stands for criticality, accessibility, recuperability, vulnerability, effects, and shock. Experts analyzing different components of the critical infrastructure served as consultants to assign scores to the CARVES components within a matrix. In this construct, people are not the target, and are essentially “in the way”, representing a potential focus of collateral damage. As an example, the bus bombings in Israel were described as an effort to primarily disrupt transportation systems, rather than targeting passengers.

The group classified high-risk biothreats into three different categories. One class consisted of the bioaerosols, viewed as weaponized agents, including such entities as aerosolized anthrax, smallpox and ricin. This category was the one most familiar to individuals with a DOD and Cold War background. A second category of bioagents encompassed non-zoonotic diseases of agriculture affecting crops, forests and livestock. Examples from this category include foot and mouth disease, classical swine fever and Newcastle disease. These agricultural diseases, whether precipitated by terrorism or naturally occurring, could have significant adverse effects on the nation’s infrastructure, as well as widespread human impact. A third category of biothreats consisted of wet bacterial, toxin and viral diseases transmitted via food, including such infections as *Shigella* and *Vibrio Cholera*.

The concept of strategic biomunitions, designed for specific non-immediate effects downstream, was an important point of discussion. Most attention to date has been focused on the potential intentional release of a weaponized bio-aerosol agent within a large population, with the resultant loss of life and associated hysteria. The group noted that other scenarios involving the non-zoonotic diseases of agriculture or food-borne agents could be equally or even more catastrophic by direct targeting of national food production. If bio-agents were found in infant formula, for example, the loss of consumer confidence could cause sustained adverse economic impact. As exemplified by the terrorist attacks on the World Trade Center, “targeting the dollar stream” is an effective way of causing chaos in Western nations.

The recent outbreak of foot and mouth disease (FMD) in the United Kingdom was reviewed. The primary infectious disease event and secondary economic effects have been well described. Delayed effects of the epidemic on other activities, such as recreational events and military training, were not appreciated until several months after the epidemic. Because some military exercises were conducted in areas inhabited by livestock, vehicles and equipment had to be disinfected, adversely affecting mission readiness.

The placement and location of biosensors were considered to be as critical as the sensitivity and specificity of the devices used. In addition, the group discussed the fact that infectious disease outbreaks, whether naturally occurring or precipitated by acts of terrorism, were an international problem, unrestricted by borders. Associated events abroad, such as excessive antibiotic use, would result in an influx of drug resistant pathogens into the US as well. Asia contains significant influenza surveillance network components because it not only constitutes a large percentage of the planet’s landmass, but also has a high human population density and animal environment conducive to the development of new strains of influenza. The fact that the SARS corona virus originated in China was not surprising.

US experience with the WNV provided lessons learned about biosurveillance data collection and utilization. The time delay in the recognition of WNV in New York City highlighted a problem with having non-integrated veterinary and public health data systems. In addition, while standardization of reporting WNV cases and the number of infected crow carcasses facilitated epidemiological data sharing among different federal government agencies, some important, unique features of the data were lost in the simplified tracking approach.

The basic question of what constitutes a biosensor was discussed. While the usual image of a biosensor is that of equipment or a device capable of detecting and/or diagnosing bioagents, the group considered a broader definition encompassing all methods of data collection that suggested an evolving biological event and “pointed the observer in the right direction”. Data from such “sensors” would include any medical or non-medical information that indicated the possible presence of, or environmental conditions conducive to, an infectious disease outbreak.

The concept of integrated biosurveillance to detect indications and warnings for a possible bioevent was also reviewed. Current biosurveillance systems fail to provide pre-event predictive information and are stove-piped across multi-sector domains. The integration of multiple data sources offers the potential for better predictive ability and greater lead-time warning than that provided by separate, stand alone surveillance modalities. Non-traditional, multi-disciplinary data sources not originally designed for surveillance purposes have great potential use and can also be exploited. For example, critical indicators and warnings for bio-events such as SARS, Ebola, and VEE have already been retrospectively identified by incorporating non-traditional data sources such as media reports, telecommunications, and socio-economic and enviro-climatic markers. The value of integrated biosurveillance will be realized when lead-time for response planning is expanded by providing pre-event alerts that enable “priming” of the national response system. Comparison of multiple data sources suggestive of a bioevent may also decrease the number of false positive alerts. Holistic integration of current biosurveillance systems to address plant, animal, and human events across foreign and domestic domains is critical to further develop this approach.

Summary Statements and Recommendations

- * Candidate biowarfare agents should be evaluated not only for their potential to cause disease and loss of life, but also for their ability to be used as strategic biomunitions capable of crippling one or more components of the critical infrastructure over a sustained period of time. Potential for mutation and the creation of pathogens with more indolent clinical presentations and the ability to elude biosensors are also important to consider.**

- * Current threat assessment regarding potential bioterrorism events, as well as recent actual infectious disease outbreaks, suggest that animal and plant health data are relevant and critical to not only public health, but also to maintenance of the critical infrastructure. Increased attention should be given to the incorporation of such agricultural information into surveillance and response strategies.**

- * Integrated biosurveillance to discern indications and warnings for infectious disease outbreaks offers the potential for increasing lead-time response. Formal research planning is needed to more fully exploit the possibilities offered by this approach.**

Chair

Peter Estacio, PhD, MD, MPH, Senior Diagnostics Advisor, Office of the Assistant Secretary for Public Health Emergency Preparedness, Department of Health and Human Services, Washington, DC

Issues Addressed by the Working Group

- * *Review and discuss the relative importance of different attributes of biosensors depending upon the intent of use of such devices*
- * *Identify strategies for optimizing the cost effective implementation of biodetectors*
- * *Identify any urgent policy or research gaps related to biosensor use for the detection of biothreat agents*

Discussion Summary

For the purpose of focusing discussion, the public health group defined biosensors narrowly as devices or methods used to detect the present of biological organisms. In general, these biosensors operate by detecting an organism's DNA or RNA, or by detecting proteins expressed by the organism. Although these were the usual targets for rapid biodetectors, measurements such as mass spectra (SELDI-TOF, MALDI-TOF), hemolytic ability, presence of chemical metabolites, and carbon dioxide production could also be exploited. In addition, newer methods of viability assessment are important in assessing the potential health risks associated with identifying the mere presence of an organism.

The group reviewed a characteristic time-line for a bioterrorist event, highlighting the enormous advantages to public health for detecting an event as early as possible. Environmental sampling and testing in relation to the incubation period of selected bioagents were discussed. In terms of the timeframe for results, immunoassays and PCR were considered suitable for biodetection, operating within a couple of hours. Although cultures have been considered more sensitive and specific than immunoassays and PCR due to their ability to manipulate an organism's replication in highly characteristic ways with a wealth of widely distributed historical experience, depending on the organism more than 24 hours can be required to obtain results. It was noted that PCR, which involves chemical replication, could potentially be more sensitive in cases of selected facultative pathogens that were difficult to grow. Information about various relevant Government projects and programs, such as the Laboratory Response Network and the Metropolitan Medical Response System, was also presented and reviewed.

The response implications of overt versus covert bioattacks were discussed. In a case involving the dissemination of infectious material heralded by phone calls or emails, for example, hazardous material response teams would constitute the first responders. Law enforcement officials would also play a prominent early role. Covert release of a bioagent would result in the presentation of diseased individuals to private and public healthcare providers. In this case, the first responder would be the astute clinician.

The group acknowledged that public health requirements for biosensors were contingent, in part, upon pathogen risk assessment. "One size did not fit all". For threat analysis, five analytical questions were delineated whose answers would place different requirements on the devices:

- * "What is it?" – identity of the pathogen dictated specificity requirements.
- * "How much is there?" – concentration of the bioagent capable of causing disease determined sensitivity needs.

*“Is it alive?” – discerning the viability status of a threat agent was critical for determining its ability to cause harm. Cultures are the only currently available test for confirming viability.

* “Is it dangerous?” – an organism’s pathogenicity and virulence were crucial for assessing risk

* “Can it be treated?” – existence of effective countermeasures such as antibiotics, antiviral medications, and vaccines was key to limiting morbidity and mortality

Biosensor requirements should also be characterized by the end user’s needs. For example, were tests being done for preventive purposes, to decide whether or not to don protective gear, or to determine a diagnosis for individuals after they became sick? Time, place, purpose, and scale were parameters useful for defining these needs. The group considered the primary use of biodetectors during the pre-event period for surveillance, during the peri-event period for screening, and during the post-event period for characterization. Place was described as field or laboratory, in a military or civilian setting. Purpose was conceptualized as related to medical care decisions, e.g. choosing medications or determining need for isolation, or environmental concerns, such as movement restriction to prevent further spread of disease. Scale referred to number of casualties for a given event: level I, <1,000; level II, 1,000-10,000; and level III, >10,000. The group noted that biosensors are most important in the public health domain for providing warning and assessment of large scale (level II/III) attacks. In level I events, the disease is most likely to be observed first by the astute clinician rather than surveillance efforts.

Fourteen biosensor parameters were delineated for consideration when developing biosensors, varying in importance depending upon the risk assessment and user’s needs for a given situation: 1) specificity - accuracy; 2) sensitivity - threshold for detection; 3) cost; 4) speed – minutes preferable to hours; 5) reliability - precision and reproducibility; 6) usability – ease of use; 7) usefulness; 8) ruggedness; 9) stand-off ability - remote detection; 10) autonomous characteristics - ideally able to run on its own >1 week; 11) ability to determine pathogenicity; 12) ability to determine viability; 13) portability; 14) throughput - samples run per hour.

For pre-event wide area surveillance of a large scale event, specificity was the consensus most important parameter. The group felt that the burden imposed by false positive tests would not be tolerated by the public health system. The next most important parameters in rank order for consideration in this setting were felt to be sensitivity, cost and speed.

In the peri-event large scale setting, determining the extent of the event, i.e., area affected and number exposed, was considered critical. Sensitivity was thought to be the most important parameter. Usability and speed were felt to be the next most important considerations. Specificity, cost, throughput and portability were listed next.

The group recognized that requirements for the post-event and recovery periods also needed to be defined. Due to the time constraints of the conference, most of the discussion was focused on the pre-event and peri-event periods. For the recovery phase, it was noted that guidelines to specify “how clean is clean enough” represented a pressing need, as exemplified by attempts to confirm decontamination in mailrooms and Congressional office buildings following the anthrax incidents. The exact identity of the organism under consideration (*Bacillus Anthracis* spores vs. *Francisella tularensis*), the form of the organism (weaponized vs. non-weaponized), and the precise location of the organism (hospital cancer treatment ward vs. cattle ranch in Texas) were felt to be critical parameters during the post-event and recovery time periods.

Given the costs associated with the development and deployment of biosensors, the concept of dual use was thought to be extremely important for long-term sustainability of biodetector programs. Identifying infectious disease outbreaks of public health significance, such as influenza epidemics or Norwalk virus outbreaks, would provide societal payback worth the initial monetary investment. It would be much harder to justify expenditures by simply stating that biosensors were protecting society because they were being used and no attack had occurred. Since many infections caused by

bioterrorism present clinically initially like common illnesses, it is imperative to provide a rapid definitive diagnostic test for the bioterrorism agent as well as the more prevalent look-alike disease-causing organism. For example, the availability of a rapid definitive diagnostic test for chickenpox or monkeypox would be as important as a definitive diagnostic test for its look-alike smallpox. Similarly, since many bioterrorism organisms present early as “flu-like syndrome”, it is equally as important to have a rapid and accurate diagnostic test for influenza as it is for anthrax. Scalable and flexible sensor systems capable of detecting a myriad of different current as well as emerging biothreats, whether naturally occurring or intentionally released, are needed. In addition, the relative rarity of bioterrorism events, in comparison to more commonly encountered public health bioagents, provides another strong argument in favor of dual use capabilities.

Another issue integral to biosensor development discussed was that of environmental versus clinical testing. Although sampled material was very different from these two environments, when a test was considered clinical could be subject to interpretation. If a swab were performed on a tabletop, for example, the sample would be considered environmental. If the same swab test were performed on a person’s nose, would it now be considered clinical? If an environmental test provides the basis for medical decisions and leads directly to a medical intervention such as administering medication, vaccination, isolation or quarantine, does that outcome in and of itself render the test a priori a “clinical test” subject to FDA regulations? These questions were considered important, as the FDA is responsible for regulating all clinical tests, while the regulation of environmental testing remains ill defined.

In a joint session with the Critical Reagents working group, issues regarding the use of different testing methods by civilian and military agencies and the lack of a nationally accepted standard for process validation were discussed. The Public Health working group voiced strong support for the recommendations advanced by the Critical Reagents group members (see Critical Reagents section below).

Summary Statements and Recommendations

*** Within the public health domain, biodetectors and biodetection systems have the greatest potential for impact by providing early warning and assessment of large scale (level II/III) attacks. Specificity is the most important attribute of a sensor during the pre-event period, while sensitivity is more critical during the peri-event period.**

*** Dual use capability is paramount for the long-term sustainment of programs developing or deploying sensors for the detection of biothreat agents. Improved public health surveillance for, and response to, high risk infectious diseases in general would provide societal payback and justify the significant expenditures associated with these programs. The ability to rapidly and accurately attribute disease outbreaks to bioterrorism agents, naturally occurring agents, or genetically modified organisms (natural or man-made) would also be facilitated.**

*** Guidelines are needed to facilitate more directed and cost effective environmental sampling and to establish adequacy of decontamination during the recovery phase of a bioevent. “How clean is clean enough” will help determine the characteristics of assays needed to direct and terminate clean-up operations.**

*** The overall challenge of biodefense is a strategic need to consolidate and unify currently disparate programs and mission priorities to develop an end-to-end response system integrating detection, clinical biosurveillance, consequence management, and medical response at the national level.**

Chair

David Cullin, PhD, Technology Director, Joint Program Executive Office for Chemical and Biological Defense, Falls Church, VA

Issues Addressed by the Working Group

- * *Discuss the role of biodetectors in relationship to the time course of a bioevent*
- * *Review current and evolving requirements of sensor devices*
- * *Identify gaps in biosensor research and development and best areas for future investment*

Discussion Summary

The working group evaluated the operational spectrum of bio-detection by focusing on different phases of a bioevent. The pre-attack, trans-attack, and post-attack time periods were chosen for review. Although the recovery period was acknowledged to be an important topic, the participants felt that the spectrum they chose was reasonable given the time allotted. Some of the participants gave presentations about their biodetector programs. The group was divided into 3 subgroups to address the different bioevent phases.

Participants noted that during each phase of the timeline, there were various recipients of the information provided by biodetectors. Each recipient was responsible for a different response. During the pre-attack period, for example, the intelligence community would be keenly interested in understanding the ramifications of pre-event measurements. The peri-event period would be dominated by the need for clinicians to make medical treatment decisions. During the post-attack period, public health officials would be involved with issues such as quarantine and decontamination, while law enforcement officials would be interested in the forensic capability afforded by biosensors. The group concentrated on developing technological objectives to support the information requirements of each of the time phases.

A common need identified for all phases of a bioattack was the requirement to integrate large amounts of different types of information. The ability of electronic information management systems to collect, organize, analyze and disseminate data from multiple sensor and non-sensor sources was considered vital. Biosensors were defined as devices that could detect the presence of biological agents, and were considered pieces of a puzzle for discerning biothreat status. In military operational settings, the group thought that other information relevant to threat assessment already existed on the battlefield, but was not yet being fully exploited. Data obtained from biosensors should be interpreted in the full context of situational awareness in all settings.

The group believed an important goal of biosensors would be for a device to have the capability to simultaneously perform multiple measurements based on different independent pathogen or toxin features, such as biomarkers or receptors. Such an orthogonal, parallel approach would improve the accuracy of the detector and increase the confidence of the information recipient. In addition, not relying on a single characteristic would be particularly important in the event an attribute of an organism had changed due to genetic alteration. The more features used for identification, the more difficult it would be for an adversary to defeat the system. Newly emerging biothreats could potentially be more easily characterized as well using a multivalent approach. A “universal” biodetector applicable to all bioagents would be the ultimate goal.

Cost was noted to be an extremely important consideration in the development and deployment of biodetectors. The group felt that commercial participation was essential, particularly for transitioning technology to the marketplace. Currently, however, private industry did not see money being made in this area due to a relatively small known user group. Designing sensors that were user-friendly would help decrease costs by creating a larger use group. Exploiting existing technologies, especially where there were infrastructures already available to support them, would help contain expenditures as well.

The need to increase the stand-alone capability of biosensors used for environmental monitoring was also highlighted. Automated systems capable of remote operation without the need for frequent human intervention would be ideal. Devices that were reagentless and consumable free would help facilitate this independence, as well as control costs.

In addition to the issues discussed above by all of the subgroups, the subgroups individually reviewed other biosensor requirements and issues they considered important. They also identified research gaps and recommended topics for scientific investigation.

The pre-attack subgroup focused on the time period preceding an actual bioevent. Members listed sensitivity/specificity, robustness, compatibility with multiple sample matrices, reliability, versatility, multiple mission capability (e.g., forensic use versus remote field operation in multiple environments), and mission-appropriate portability as additional salient characteristics of biodetectors. The group felt that methods to extract and concentrate samples constituted an important area of needed research, but were often forgotten, in part, because this type of investigation was not as compelling as developing more accurate technology for disease detection. Capturing, purifying and in some cases transporting material was critical for accurate diagnosis. Other suggested research focus areas included: automation; miniaturization; improved signature recognition of illicit activity; improved transducer technologies; elucidation of agent-specific biochemical reactions; and improved biorecognition elements, such as high affinity/avidity receptors with high specificity.

The trans-attack subgroup reviewed the requirements of biodetectors that functioned in a manner analogous to smoke detectors, first alerting the system that something was actually happening, as well as those that performed confirmatory identification. Desirable features identified for environmental “smoke detector-like” trigger devices included stand-alone, consumable free, easy-to-use, useful for all potential threats, and yielding immediate results. For environmental or clinical sensors used to perform confirmatory identification, requirements listed were high specificity, laboratory level equipment, trained operators, near real-time results (less than 1 hour) and low throughput/low number of samples processed. After reviewing the properties of current systems, participants defined research gaps to be addressed. Suggested areas of investigation for trigger devices included biothreat agent signature definitions and libraries, spectroscopic techniques involving new regions of the electro-magnetic spectrum, open air design, improved sensitivity and selectivity with understanding of pathogen background levels, and creation of device standards for sensitivity and false alarms. For confirmatory devices, recommended focus topics included: faster and more efficient collection and preparation procedures that maintained viability of samples from various different matrices (air, water, soil, etc); quicker and orthogonal analytical platforms; methods that decreased/eliminated consumables; and establishing standards for validation of environmental or clinical analytical methods used (through an organization such as the Association of Analytical Communities or the Food and Drug Administration).

The post-attack subgroup reviewed the current status of, and identified areas of needed research for, sample collection, sample analyses, and decision analysis. Desirable approaches to sample collection listed by the subgroup included use

of non-invasive medical devices (e.g., breath analyzer or optical vascular scanner), dual use for non-terrorism related infectious disease outbreaks, use of evolving technology such as that combining sample collection with pre-analysis screening, and “lab on a chip” total systems. They also favored a general overall increase in the amount of environmental and medical surveillance being done. Important areas of needed research identified were improved methods for extracting, concentrating, stabilizing and transporting specimens. Issues involving standardization and verification of forensic processes, as well as chain of custody, were also noted as unresolved. For sample analysis, adaptable systems that could test samples without a priori knowledge of bioagents were considered the goal. In addition, the study of emerging spectroscopic and spectrometric technologies and the development of systems requiring fewer consumables should be encouraged. Recommended focus areas for research included: development of automated and mobile systems; reduction in analysis time; increased user-friendliness; multi-valent capabilities to detect a variety of biothreat agents and toxins; improved pathogen signature definition with expansion of libraries; and standardization and verification for accreditation of analytical methods. To support decision analysis, imbedding intelligence in an information management system was considered key. Telemedicine and wireless technology were discussed as emerging contributors to this process. Needs identified included consensus regarding decision-making and comprehensive, integrated information management systems that would facilitate timely dissemination of information for decision support and allow mining of existing data. The use of disruptive technologies was favored by the post-attack subgroup as a whole for advancing biosensor research. MEMS, proteomics, nanotechnology, bioinformatics, and *in vivo* analytical tools (to assess host response) were cited as examples. Participants acknowledged, however, that further discussion was needed within the scientific community to determine the optimal research investment strategy.

Summary Statements and Recommendations

*** Biosensors that perform orthogonal detection with parallel measurements should be developed. Such a design would enhance accuracy and decrease the probability that pathogens or toxins would avoid detection.**

*** Biodetector data reporting should interface directly with electronic information management systems. To maximize utility, these systems should be capable of collecting, integrating, analyzing, and disseminating information relevant to threat assessment from multiple different sensor and non-sensor sources.**

*** Cost is a significant concern in the development and implementation of biosensors. Efforts to decrease device consumables, develop autonomous devices, exploit existing technology, and provide dual use should be pursued.**

*** Improved methods of sample collection, processing, and stabilization represent critical needs currently undervalued and under-represented in most biosensor research programs.**

*** Standardization and validation of environmental and clinical analytical methods are needed. Guidelines for the use of biosensor results in decision-making also need to be developed.**

CRITICAL REAGENTS

Chair

Peter Emanuel, PhD, Joint Program Executive Office for Chemical and Biological Defense, Critical Reagent Program Director, US Army Edgewood Chemical Biological Center, Aberdeen Proving Ground, MD

Issues Addressed by the Working Group

- * *Discuss advantages and disadvantages of standardizing how reagents, tests and methods are validated and utilized*
- * *Propose ways to establish a nationally accepted process for validating tests and methods*
- * *Identify problems that will be encountered on this drive towards a nationally accepted validation process*

Discussion Summary

The critical reagents working group focused on an identified urgent problem related to the use of environmental monitoring devices. The Laboratory Response Network (LRN), under the direction of the CDC, has a standardized system of assays and protocols applied nationwide, such as those employed in the DHS BioWatch Program. The DOD maintains similar programs, but uses different assays and protocols. Planned expansion of a current DOD joint service installation pilot program would include the surveillance of civilian areas, regions traditionally protected by the LRN. Such initiatives magnify the differences between the DOD and CDC, the largest consumers of environmental sensing technology, with some agencies not at liberty to accept each other's data.

A distinction was made between environmental sampling systems and diagnostic clinical assays. Issues involving the latter are addressed by interagency working groups sponsored by the Office of Science and Technology Policy (OSTP), Executive Office of the President. Although the primary focus of OSTP is clinical, concerns related to environmental monitoring could impact clinical care decisions, implying that the issue of non-standardization would be of relevance to OSTP as well.

Ensuring test results from the civilian and military sectors are mutually acceptable has become critical as the country works together to develop a national strategy for biodefense. Standardizing how reagents, tests and methods are validated and utilized is a necessary step toward realizing this goal. Creating a nationally accepted process for this validation will increase confidence in our ability to provide reliable information, and will enable the movement of new assays and platforms in a timely and quality controlled manner. More efficient utilization of time, personnel, funding and consumable resources will also be facilitated as the need for redundancy in testing is eliminated.

The working group reached a consensus that an interface among invested military and civilian government agencies should be created to evaluate environmental monitoring samples for biothreat agents, to ensure that results are comparable and acceptable to all parties for use in consequence management. Suggested concrete steps are listed below and constitute the beginning of a process that will be based on this agreement, called the Morningside Accord. The DOD's Critical Reagents Program (CRP) and the CDC's Laboratory Response Network (LRN) have begun to act on the goals laid out in the Morningside Accord and are developing systems for the long term cooperation and leveraging of resources between these programs.

Summary Statements and Recommendations

- * **Establish a Memorandum of Understanding between key players such as the DOD, DHS and DHHS/CDC.**

- * **Exchange process criteria and data generated from each process.**
 - o Define and standardize terminology used to describe processes.
 - o Describe methodology detailing validation protocol for each assay.
 - o Provide data for each assay subjected to this procedure.

- * **Exchange reference samples to compare assay results, in support of the interoperability of programs.**

- * **Based on initial exchange of samples, establish an ongoing process for sample exchange for reference testing.**
 - o Programs test according to their established assay protocols.
 - o Testing is outcome based.
 - o A process for arbitration of discrepant results is defined.

- * **Continue the above process for evaluating new technologies.**

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