

STRATEGIC ACTIONABLE NET-CENTRIC BIOLOGICAL DEFENSE SYSTEM

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Abstract: Technologies required for strategic actionable net-centric biological defense systems consist of : 1) multiplexed multi-array sensors for threat agents and for signatures of the host response to infection; 2) novel vaccines and restricted access antivirals/bacterials to reduce emergence of drug resistant strains pre- and post-event; 3) telemedicine capabilities to deliver post-event care to 20,000 victims of a biological strike; and 4) communication systems with intelligent software for resource allocation and redundant pathways that survive catastrophic attack. The integrated system must detect all threat agents with minimal false positive/negative events, a seamless integrated broad-band communications capability that enables conversion of data to actionable information, and novel pre- and post-event treatments. The development of multiplexed multi-array sensors, appropriate vaccines and antibiotics, and integrated communication capabilities are critical to sustaining normal health, commerce, and international activities.

1. INTRODUCTION

The overarching objectives in developing effective countermeasures to biological threats are to protect the Defense community and citizenry from such threats, and to develop agile responses to unanticipated events considering that successful terrorists do the unexpected. The need for protection against and responses to biological threats has been strikingly demonstrated by the use of anthrax contaminated letters that were sent through the U.S. mail in October 2001. That attack resulted in human illness, the loss of life, and discontinuity of government operations because of contamination of federal office buildings in Washington, DC. A recent report prepared by the Center for Strategic and International Studies (CSIS) and supported by the Defense Threat Reduction Agency (DTRA) of the

Department of Defense (DoD) came to the conclusion that the U.S. is at present not well prepared for a similar attack using anthrax¹. The major problems include a lack of: 1) a clear chain of command, and 2) tools to provide the public with information that permits appropriate responses.

The incidence of Congo-Crimean hemorrhagic fever in Afghanistan, an area where coalition forces are being deployed, increases this need. The potential threat posed by emergent disease (e.g., Severe Acute Respiratory Syndrome [SARS] and West Nile Fever virus) or from a major release of a contagious biological agent such as smallpox, has been a growing concern at all levels of the international community. This article outlines and discusses a new strategy that is needed if we are to be fully capable of sensing, preventing, and managing biological threats.

2. NEW PARADIGM

The current paradigm addresses biological and chemical terrorist threats in a vertical (stove-piped) response. In the arena of developing sensors for the detection of biological agents, the paradigm has been to develop separate detectors for each agent or to develop a platform for detecting 12-24 threat agents using a single probe for each agent. There is a lack of an interactive networked communication system that is capable of managing a devastating emergent disease. To establish a highly networked system that is rapid enough to permit effective protection, it is necessary to evolve from the stove-piped, compartmentalized model currently in use to an integrated, fused, probabilistic, and frequently updated information model. Multiplexed multi-array sensor systems, capable of recognizing all bacterial or viral genomic materials related to pathogenicity or of recognizing antigenic domains that are specific indicators of pathogens are one component of a network needed for rapid detection and identification of biological threats. With respect to therapeutics, modern technologies for vaccine and antibiotic production provide decided advantages over older methods. The traditional vaccines require extensive development times before they become available for human use and undesired side effects commonly result from vaccines produced by these protocols. The cost associated with developing and testing vaccines, using traditional technology, approximates 50-100 million dollars per vaccine. The dissemination of antibiotics and antivirals through the world markets has resulted in the appearance of pathogenic bacteria and viruses that are resistant to these drugs. One approach to reduce the development of antibiotic resistance is to restrict the distribution of newly developed antibiotics. Such an approach presents ethical and social dilemmas. The consideration of options available for reduction of drug

resistance, prior to a threat event, may permit development of a rational policy. A major problem facing our nations in the event of a biological attack or emergent disease is the large numbers of patients that can be anticipated to require medical treatment. Although improvements in emergency medical care and hospital equipment have been achieved during the past two decades, the ability of any community to manage an outbreak of infectious disease affecting >10,000 people is lacking. Rapid progress has been achieved whereby medical care can be provided to patients at sites that are distant from primary caregivers using telecommunication systems (e.g., the Armed Services in theater, large scale HMO providers such as Kaiser Permanente, or the correctional institutions in the U.S.). The funds needed to acquire telecommunication equipment for such distributed medical care delivery are estimated to be less than 100 million dollars for the entire U.S. At the present time such a distributed care system is not readily available.

The new paradigm couples a network centric integrated sensor alert system that can detect all threat agents simultaneously, with a seamlessly integrated communication software capability that converts large scale data to actionable information. For this to be effective, the sensor system must yield minimal false positive and false negative results. The new paradigm incorporates large-scale databases on normative values of threat agents in many regions of the world so that significant changes in real time can be detected. The paradigm also includes the development and implementation of novel pre- and post-event treatment capabilities.

Attention must be paid to the ability of high level decision makers and operators to recognize that a new state of threat has emerged, based upon output of the sensors, data fusion system, and iconographic display. Ambiguity of data, lack of an autonomous processing system, and high stress on the operator (e.g., sleep deprivation, lack of training) may all compromise the utility of a highly networked system of systems. What is needed for this new paradigm to succeed? The needs include multiplexed multi-array sensors for biological agents that infect people, livestock, and edible crops. The agents of concern include many on the Militarily Critical Technologies List prepared for the Office of the Secretary of Defense. We need multiplexed multi-array sensor systems with high specificity and selectivity for the rapid detection of host responses to infection. We need a new generation of effective therapeutics, including vaccines, antibiotics, and antivirals. A network centric intelligent communication system that can provide accurate comprehensible information to decision makers (from command officers to unit operators) is required. To minimize morbidity and mortality and optimize containment of disease, a biosurveillance system based on archival health databases, statistical models, and data mining strategies that can provide an early alert to a disease outbreak is required.

In many cases the operator may be required to understand the meaning of acquired data in very short time periods (seconds to minutes) if the response is anticipated to change the outcome of an engagement. The Tactical Decision Making Under Stress (TADMUS) program is one example of such a situation. In the biological threat arena, the detection and identification of toxins require rapid analysis and operator comprehension. The large increase in numbers of sensors (for high explosives [HX], biological and chemical agents, meteorological conditions) together with the rapid changes in op tempo required to manage emergence of clinical disease would suggest a need for the development of systems capable of autonomous generation of an alert when threat conditions arise.

3. CURRENT STATE OF TECHNOLOGY NEEDED FOR THE NEW PARADIGM

In the sensors area, the genomes of most biological threat agents have been sequenced and the signatures of toxins described. Novel multiplexed multi-array sensor-platform systems utilize the genomic datasets to detect the appearance of threat levels of these agents. In the therapeutics area, researchers are working towards identifying critical antigenic epitopes of these agents. New therapeutics can emerge that have an antigen binding capacity significantly greater than antigen-cell receptor binding, resulting in the potential for agent neutralization. Technologies have been developed over the past decade for the development of new drugs and DNA based vaccines. Restricted access antivirals/antibacterials will need to be developed to reduce the emergence of drug resistant strains pre- and post-event.

A significant development in our program at The University of Texas at Austin (UT-Austin)² has been the novel design and production of an antibody that binds the anthrax PA antigen 1000 times stronger ($K_d < 10^{-11}$) than any antibody to date. The antibodies were produced using phage display technology for selection of the antibodies. In tests with experimental rodents in a controlled facility, administering the Bacillus anthracis PA antigen to the animals resulted in 100 percent fatalities, whereas the co-administration of the newly developed antibody against the PA antigen resulted in 100 percent survival². Research is also being conducted to determine unique nucleic acid sequences in the genome of pathogenic bacteria and viruses that contribute to the pathogenic properties of the organisms. This information is being used to develop multiplexed assay systems that can detect selected agents simultaneously. By quickly screening for multiple pathogenicity island sequences or pathogenic factors, end-users will have the capability to detect the first signs of emergent disease without requiring screening for

each particular organism. In the communications area, researchers are developing ‘belief maintenance’ software to provide decision makers some estimate of the validity of incoming data. An estimate of information credibility is critical to effective decision-making in crisis situations when one must rely on an 80 percent solution (i.e., 80 percent of needed information is available). Waiting for a 100 percent solution could have a catastrophic impact on response effectiveness.

In the area of telecommunications, researchers are developing the means to provide effective medical triage to victims in a contaminated hot zone. The hot zone in this case refers to a region experiencing an outbreak of a highly contagious disease that causes death in a significant percentage of infected individuals. Advanced telecommunications technology can permit physicians and other medical experts at remote locations to provide medical information and support care delivery to personnel in the hot zone. Prior training of these personnel (from physicians to local citizens) is required. An extensive use of local persons will be necessary if it is deemed inadvisable to introduce health care workers and communications experts into the hot zone; the external support teams are required to provide ‘back-fill’ support to the overburdened local community.

Biosurveillance systems are being developed to serve as an early warning of emergent disease. A variety of databases are being developed that are health related. Examples of these databases include school absenteeism, over-the counter drug sales, hospital emergency clinic visits, and archival records on the incidence of diseases in different geographic regions, CONUS and OCONUS. Each database must be statistically characterized regarding parameters such as variance, confidence intervals, seasonality, etcetera, and be integrated into validated predictive models. Once the reference databases are in place and suitably modeled, statistically significant departures from baseline values can be detected and transmitted in real time to decision makers through intelligent communication systems.

3.1 Technology Gaps

A number of critical technology gaps exist that must be addressed if we are to recognize, prevent, and minimize the effect of biological agents. These gaps include: deficiencies in the availability of multiplexed multi-array agent sensors and platforms; critical reagents; capability for large-scale production of effective vaccines, antibiotics and antivirals; ability to treat a large number (10,000) of infected people 24/7 for several weeks in a biological hot zone; archival biosurveillance databases and intelligent and secure communications networks. With the new capabilities and devices anticipated during the next decade, approaches that address these gaps include the use of

autonomous (e.g., cell phone-based) microelectronic detectors for the transmission of data on agent exposure, development of novel antibodies, antibiotics and antivirals to manage disease outbreaks, and establishment of global surveillance systems for emergent diseases (e.g., SARS, West Nile Fever, Congo-Crimean Hemorrhagic Fever).

3.2 Research Areas

Because of the broad scope of needs for technology to prevent and minimize biological threats, a number of research areas have been identified as critical. These include: the scientific validation that a biological incident has occurred (requisite tools/capabilities include situation awareness systems, sensors and signatures); the availability of medical countermeasures (vaccines, pharmaceuticals, and medical transport); and a highly effective communications network for the secure transmission of data and the conversion of such data to comprehensible information so that decision makers can take appropriate actions.

3.3 Sensors Research

For effective sensors, a variety of materials are being developed that include effective high-affinity binders of biological threat agents. The high affinity binders include antibodies, cDNA gene probes, polynucleotide aptamers, and combinatorial chemicals. Using phage display methods, antibody fragments can be selected that have a high affinity for agents such as anthrax toxin and brucella. Another binding system that has been examined uses polynucleotide aptamers about 31 nucleotides long that have good binding affinity to ricin toxin. These sensor materials require opto/electronic transduction platforms. Sensor platform research currently is being focused on micro-electro-mechanical systems (MEMS) devices, microelectronics technology, microfluidics (laboratory-on-a-chip), DNA/protein microarrays, and transduction devices. Efforts are also being directed toward the development of multiplexed multi-array systems that detect approximately 100 biological threat agents of concern. For military application, it is essential that sensor systems can detect and identify agents present in samples rapidly, using platforms that are small and have low power requirements.

3.4 Therapeutics Research

With current approaches, the development-to-market of new vaccines, antibiotics, and antivirals is in the order of 5-10 years. A paradigm shift to

newer culture and DNA-based technology is needed if we are to have an effective response to a major biological or chemical event. Current estimates regarding the time required for developing and fielding new vaccines and antibiotics/antivirals to specific threat agents, using new technology and expedited approval, is in the order of three years.

3.5 Communications Research

While current computer/informatics research includes the development of telecommunications assets, a critical need in the communications area is the development of seamless integrated communication networks. These network centric systems enable the conversion of data to actionable information. Research is being conducted to provide intelligent agent software designs for such communication systems. This will enable an enhanced accuracy in critical decision-making and resource allocations. The integrated system must have redundant pathways that can survive a catastrophic attack. The communication system must be capable of integrating data on an emerging threat in a timely manner, and provide useful information for public safety coordination and perimeter management.

3.6 Telemedicine Needs

Telemedicine capabilities can aid in the delivery of post-event care to 10,000-20,000 victims of a biological strike in a densely populated area for 24 hours a day, seven days a week, for several months. In the event of smallpox attack in which 10,000 people develop clinical symptoms of infection within 7-10 days following exposure, local hospitals and medical response capabilities would be overwhelmed if current treatment protocols were used. Telemedicine allows physicians at a remote location from the hot zone to provide medical support via telemedicine capabilities (visual, audio) to aid local physicians in treating patients. A treatment level of 50 patients per day per physician would require 200 physicians to provide telemedicine care for 10,000 patients. Each physician would require telemedicine devices; hence 200 telemedicine devices would be required at the remote location, and a similar number in the hot zone. A national telemedicine system could include the establishment of approximately eight telemedicine response centers nationally, interconnected via satellite to telepresence and telemedicine/robotic systems. The remote care capability reduces the likelihood of the dissemination of disease to physicians and communities in which the physicians reside. A telemedicine system would also retain health care delivery in communities providing health care back-fill.

3.7 Networked Operations at the Coordinating Level and Lower Echelons of Command

A decision making component is required for coordinating the delivery of actionable information. Figure 1 illustrates such a flow chart. In threat situations, data developed from sensor arrays, surveillance systems, and therapeutics inventories can be electronically encrypted and transmitted via intelligent communication networks to decision makers for appropriate actions. The decision makers include individuals, government authority, medical care experts (doctors, hospitals, the Centers for Disease Control and Prevention [CDC], etc.), and the military.

3.8 Network Centric Response to Threat Data Fusion and Human

1. Perception/Comprehension
2. Primary issue of concern
3. Full situation awareness is contingent on at least four elements including:
4. Large scale acquisition of data (i.e., SIGINT, MASINT, HUMINT, sensors)
5. High fidelity communication of data sets to autonomous processing centers
6. Data fusion involving weighting of data and marked reduction in data volume to yield information that provides users a common operational picture
7. Rapid comprehension of time dependent information by operators facilitated by new iconographic displays, training, measures of vigilance

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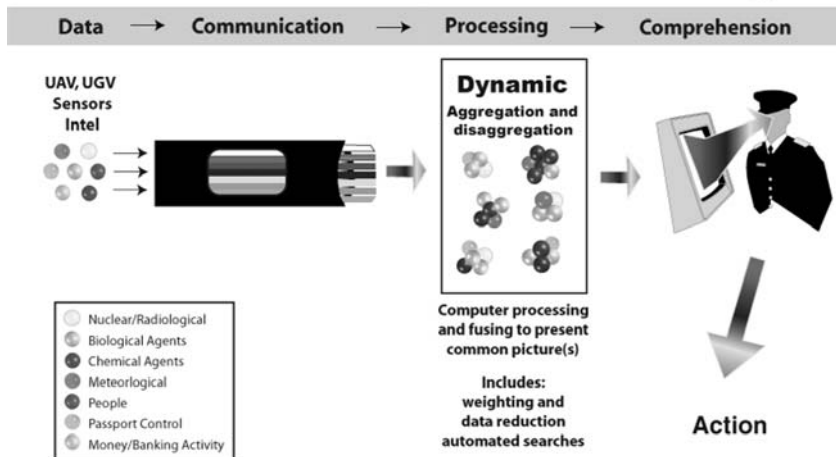


Figure 1.

3.9 Proposed Goal of the Autonomous Data Processing

The end goal is achievement of a rapid appropriate action in response to detection of threat (within minutes of threat identification). In order to meet this time constraint in a real world scenario, it is probable that the man-in-the-loop may have a denial capability rather than an approval function.

3.10 A Strategy to achieve this Goal

The tools required for autonomous weighting of data and subsequent reduction of data elements for particular missions remain to be developed and agreed upon. The technologies required for data acquisition, communication, and autonomous processing fundamentally differ from that required for comprehension by an operator. The three technologies are systems that must be developed prior to deployment and will have known probabilities of accuracy and reliability. The fourth element involves the training and state of vigilance/alertness of the operator as well as the development of software (e.g., icons, data mining, and compression) used to display threat conditions. The point of the fourth element is to permit an operator to have rapid comprehension of the state of threat in a rapidly changing environment. Because there is a time factor involved in the comprehension of threat conditions by an operator, and in the translation of the information into action, the fourth element must include temporal qualities. Since the time dependence (seconds to minutes) of an intense

threat situation will differ from that involved in a peacekeeping or supply distribution situation (many minutes to hours on the average), the autonomous weighting factors and data reduction factors can be expected to vary widely. This variability complicates programming of autonomous systems.

3.11 Basic Principles of Human Decision Making Under Stress

Command teams on the modern information-age medical delivery front face an increasing variety of cognitive stressors: information ambiguity, information overload, fatigue, and fear of contagion and quarantine. There is a requirement for a useful, predictive model of the effect of these stressors on individual and collective cognition within the medical delivery team. A model to quantify stress experienced by the caregiver and to identify countermeasures and mitigators of stress, develop organizational strategies for optimum performance under stress is needed. Psychological assessments that can predict individual and team cognitive functioning and physiological markers that can determine quantitatively and objectively the effect of stress experienced on an operators vigilance have been identified (Table 1). The identification of specific physiological markers that are predictive of stress-induced changes in complex cognitive functioning will aid in the construction of autonomous weighting systems.

Table 1. Stressors and Measures

	Stressors				
Measurement Technologies	Information Ambiguity	Information Overload	Fatigue	Social Isolation	Danger
Cognition	+++	+++	++	++	++
Behavioral Markers	+	+	+	+	++
Emotional Assessment †	+++	+++	+++	++	+++
Observer/Controller Ratings	+++	+++	+++	++	++
Auditory/Visual Evoked Potential (P300, P600)	+++	+++	+++	+	++
Respiration / Ventilation Rate	++	++	+	+++	+++
Cardiac q-t Interbeat Interval	+++	+++	++	+++	+++

+ Degree of reactivity to measurement

† (e.g., Voice Stress Analysis)

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REFERENCES

1. Lessons from the Anthrax Attacks: Implications for U.S. Bioterrorism Preparedness. CSIS Funded by the Defense Threat Reduction Agency of the Department of Defense. David Heyman investigator. March 2004.
2. Maynard, J.A., Maassen, C.B.M., Leppla, S.H., Brasky, K., Patterson, J.L., Iverson, B.L., and Georgiou, G., "Protection against Anthrax Toxin by Recombinant Antibody Fragments Correlates with Antigen Affinity," *Nature Biotechnology*, vol. 20, pp. 597-601, June 2002.