

Biological Warfare War Game 99-1

Assessment

I. Introduction. Biological Warfare War Game 99-1 (BIO 99-1) was conducted on January 20, 1999 by Wargaming Division, Marine Corps Warfighting Laboratory (MCWL) at Quantico, Virginia. A broad spectrum of scientific, clinical, and operational experts were assembled to assess a proposal presented to the MCWL by Battelle Corporation for a new approach to force protection in a biologically hostile environment. BIO 99-1 also sought to assist the MCWL in formulating a course of action regarding the Battelle initiative as part of a more comprehensive program of addressing biological warfare issues. Participants included representatives from the MCWL, the Marine Corps Combat Development Command, the Chemical-Biological Incident Response Force, the New York City Fire Department, and other government and civilian organizations. A list of participants is at enclosure (1).

II. Objectives. The specific objectives of BIO 99-1 were:

- A. To examine the advantages and disadvantages of the Battelle approach from a scientific, clinical, and operational perspective; and
- B. To provide a net assessment, conclusions, and are recommendations concerning the approach.

III. Game Methodology. BIO 99-1 was a seminar game structured in terms of **Blue Team/Red Team** interaction, as illustrated in Enclosure (2). As noted, in the first move, two **Blue Team Cells** examined the scientific/clinical and the clinical/operational advantages of the proposal. Participants in each cell identified key factors essential to success in each case. In the second move, each group became a **Red Team** and examined the previous results of the other **Blue Team**. The **Red Teams** considered disadvantages of the Battelle approach, with respect to scientific/clinical and clinical/operational feasibility. BIO 99-1 was designed to maximize the time available, while allowing for a thorough review of the Battelle proposal.

IV. Summary of the Battelle Proposed Approach. The Battelle proposal advances a radically different approach to current biological agent defense that is based on non-specific immunity as apposed to the use of external MOP gear. Specifically, Battelle proposes to develop an immunoprophylactic cocktail that would provide non-specific immunity to the user. This cocktail would consist of a combination of existing, FDA approved drugs: Interferon-gamma, Interleukin-2, Granulocyte-marcophage colony stimulating factor, and a complement activator Zymosan. The focus of the immunoprophylactic cocktail is to boost non-specific immunity, in the lungs and nasal passages, to protect against airborne biological warfare agents. More detail concerning each of these drugs is provided in enclosure (3).

The Battelle approach seeks to:

- Develop rapid acting medical protection against a wide range of biological warfare agents;
- Provide a non-invasive technique for delivery (e.g. nasal inhaler);
- Furnish protection for six to twenty-four hours following a single application;
- Supplement existing medical defense measures; and
- Provide a Federal Drug Administration (FDA) licensed product.

Furthermore, the Battelle proposal outlines an approach for evaluating the four stimulators of non-specific immunity against three potential biological warfare agents: Bacillus Anthracis (Anthrax); Yellow Fever Virus; Venezuelan Equine Encephalitis; and a common cause of respiratory disease in that occurs in the elderly, Chlamydia Pneumoniae.

In summary, then, the Battelle approach seeks to enhance the body's immune response to provide protection against a broad spectrum of biological warfare agents.

V. Findings

In this section, the advantages and disadvantages of the Battelle initiative are provided.

a. Advantages

Participants agreed that if the Battelle approach could be successfully developed, then the following scientific, clinical, and operational advantages could accrue.

- **Scientific**

The participants agreed the concept of a non-specific immunoprophylactic was advantageous for military and civilians faced with a potential biological hazardous environment.

The product described in the proposal highlighted a need in the area of biological warfare defense. The use of a broad-spectrum immunity to protect forces engaged in biologically hazardous environment is better than attempting to vaccinate by invasive techniques (injection) against every known biological agent. For example: Anthrax vaccination requires a series of six injections, to provide a 90% immunity level in the individual. Finally, such a product would preclude the need for more extensive MOP equipment.

- **Clinical**

Route of Delivery. The approach of using either an inhaler or nasal spray compared with the current methods of injection would enhance the acceptance by the operational forces. It also provides an immediate local effect in addition to the systemic effect, which current vaccines do not provide. This method of delivery also provides a simplification of post-incident /

consequence management when authorities are confronted with a large population that had been exposed to a biological agent.

Local and Systemic Effect. There are indications that introduction of the compound by use of an inhaler or by nasal spray has the potential to provide an immediate local effect in boosting immune response. The systemic effects using this route of delivery appear to be much quicker (hours instead of days) whereas vaccines could take several days to weeks to provide systemic immunity.

- **Operational**

Counters to the Threat. This product could render the production of biological warfare agents difficult to produce and field. Therefore, this product could potentially create a new deterrent against biological warfare and bio-terrorist activities.

Dual Use. This product would have dual use capability – military and civilian – for the United States.

Increased Public Confidence and Psychological Benefits. The Battelle non-specific immunity cocktail could significantly improve troop confidence and therefore moral when faced with a biological threat.

b. Some Key Factors Necessary to Make this Work

The following key factors were identified by the participants as necessary for this approach to work:

- **Systematic Implementation.** A comprehensive program of implementation is needed to allow for an incremental, phased approach to development. The program would be monitored at each phase to insure that it was moving in an acceptable manner toward its stated objectives.
- **Use of Surrogate Markers.** The research, studies, and testing, particularly with the use of animal models, will require the use of surrogate markers (non-human) to determine the validity of the concept.
- **Cost and Availability.** The product has to be made readily available at a reasonable cost and not require significant logistics support infrastructure.
- **Acceptable Adverse Reactions and Side Effects.** The product has to have minimal impact on the operational capability of operating units. Adverse reactions and side effects must be at a level that does not degrade the ability of operational forces from completing their mission.

c. Disadvantages

During the Red move, participants were asked to consider the disadvantages of the Battelle proposal. The consensus was as follows:

- **Scientific**

Participants agreed that there are two distinct scientific disadvantages to the Battelle approach:

Very Low Probability the Concept Will Work. Boosting immune responses by the introduction of a mixture of drugs in a cocktail is currently an expanding, but very immature science. Although a bold concept, the participants were very skeptical that the Battelle approach, in its current configuration would work.

Paucity of Scientific Data. The proposal presented by Battelle provided a limited amount of literature based data that suggests the Battelle approach could work. However, there is virtually no empirical data to support the contention that a combination of drugs to boost immune response, particularly in aerosol delivery, would ever work.

- **Clinical**

The clinical disadvantage of the Battelle approach revolves around three critical issues:

Significant Side Effects of the Proposed Drugs. Individually, the proposed drugs have very debilitating side effects. For Example, Interferon-Gamma has been known to cause fever, muscle pain, and nausea and vomiting; Interleukin-2 can cause severe hypotension, pulmonary edema, and headache; and, GM-CSF can cause significant bone pain and lethargy. Overall, these drugs could clinically cause the following in one to ten percent of the population using the product.

- Hypotension (rapid decrease in blood pressure)
- Fatigue
- Nausea
- Pulmonary Edema (excessive fluid in lungs)
- Shortness of Breath
- Low Platelet Counts (adverse effects on blood clotting)
- Immunosuppression

The side effects of this product, then, would be unacceptable in an operational environment.

Synergistic Effect of the Drugs. The aforementioned side effects of the drugs were considered on an individual drug basis. What will be the synergistic effect of these drugs when mixed? In the absence of authoritative data, one should assume that the mixture of these drugs *could* significantly increase the incident and severity of these side effects.

Drug Interaction. Three of the four drugs have documented drug interaction properties. For example: Interleukin-2 has shown increased toxicity of narcotics, such as morphine and in analgesics, such as Motrin. The implication of this situation is that a normal dose of commonly used medications (e.g., pain killers), may cause significant clinical problems in someone who has used the cocktail. Once again, this situation would pose serious implications to troops in the field since these medications, e.g., painkillers, are some of the most commonly used to treat injuries.

Immunological Effect. The premise the Battelle approach that these drugs individually could produce an immunological effects is seriously flawed. The Battelle proposal indicates that these drugs are anti-viral, anti-bacterial, and anti-fungal, when in-fact in many cases there is no immunological effect. The following examples apply:

1. GM-CSF does not itself have anti-bacterial properties *in vivo* (laboratory setting). It does help patients who do not have an adequate number of granulocytes, but studies in normal patients and burn victims have not demonstrated a clinical increase in bacterial kill.
2. GM-CSF does not help kill fungi in normal donors. In patients without blood cells there may be a slight advantage in activating some cells to clear certain non-lethal fungi.
3. GM-CSF has no effect whatsoever in altering viral loads or activity in humans.
4. GM-CSF takes 2-4 days before it has any biological effect.
5. IL2 has no anti-bacterial, antiviral, or anti-fungal effect in humans.
6. IF does not clear viral loads in pharmacological doses; it is anti-viral in the lab, not in people.
7. IF has no anti bacterial or anti-fungal properties in humans.

The clinical picture for use of the proposed cocktail could cause immunosuppression, not boost the immunity, as presented in the proposal. In sum, Battelle's premise is seriously flawed.

- **Operational**

Logistics/Health Services Support Concerns. This product, primarily because of its side effects, could require significant increases in logistics/Health Services Support capability. For example, it may require special handling (e.g. refrigeration) or it may not be able to be stored aboard ship due to hazardous cargo restrictions on aerosol. Forces taking this product would have to be clinically monitored (e.g., blood tests for low platelet counts,) thus increasing the need for additional laboratory capability. Additional drugs would have to be provided to overcome side effects (e.g., anti-nausea). If these concerns become a reality, additional force structure would be needed to accommodate the operational use of this product (e.g., corpsman, laboratory personnel).

Post Exposure. There were major concerns expressed by participants regarding the long-term effects of using this product, e.g., infertility.

VI. Net Assessment

- **Scientific.** While there is a potential for a body of scientific data to be collected from continued research in this area, participants believe that the probability is very low that this initiative would ever result in a product that is effective against biological weapons.
- **Clinical.** The clinical disadvantage of this product, as outlined above, would preclude its use in any operational setting. In addition, there is a very low probability the product would in-fact work against the biological agents outlined in the Battelle proposal. One participant summarized the use of this product as having no clinical advantage in any military operational situation.
- **Operational.** Participants agreed that to use this product in the field would necessitate additional logistics/health services support infrastructure. There would be a potential need for increased laboratory and health services support personnel to monitor and assist in coping with side effects or drug reactions. Finally, the side effects the drugs would clearly have an operational impact that would be unacceptable.

The result of this net assessment leads to the following conclusions:

- That the scientific and, particularly, the clinical disadvantages of this product clearly outweigh the advantage.
- That the product poses significant adverse operational impacts that would preclude its use in combat environment.
- That additional logistics/health services support infrastructure would be required to field this product

Participants agreed that while there is a great deal to be learned from research in this area, the science has not mature enough for the Marine Corps to expend resources on continued research. Participants further agreed that the Battelle initiative, at this point, should be submitted to an agency more suited to this level of research and evaluation, e.g., National Institute of Health. Participants also suggested that if Battelle truly believes that this product will work, they should undertake the research, perhaps in conjunction with the pharmaceutical industry.

VII. Recommendations

Based on the findings and conclusions, the following recommendations are submitted:

- That the Marine Corps not become involved with the Battelle proposal except to monitor the progress of the research and development effort.
- That the Marine Corps suggest to Battelle that they pursue agencies better suited to what Battelle is trying to achieve, such as NIH.