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Science and Technology Report No. 1

The United States National Institute of Allergy and Infectious Diseases (NIAID) Research Programme on Biodefense: A Summary and Review of Varying Assessments*

by

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*Study carried out under the *Domestic Management of Terrorist Attacks* (King's College, London) section of the Economic and Social Research Council, UK, *New Security Challenges* programme.

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Summary

Since the anthrax attacks of 2001 the United States National Institute of Allergy and Infectious Diseases (NIAID) has received a vast increase in funding for biodefence work. The objectives and progress of this work are described in detail for Catogory A agents such as anthrax, smallpox, plague, botulism, tularemia and viral haemorrhagic fevers and for Category B and C agents such as inhalation bacteria, arthropod-borne viruses, toxins, food- and water-borne pathogens, and emerging infectious diseases.

The work carried out by NIAID has come under criticism from two groups in the United States. The first group argues that what is being done is quite inadequate as the NIAID does not have the expertise to go beyond research and produce useful means of detection, protection and treatment. It also contends that the threat is much more serious and wide-ranging than NIAID believes. This group has strongly urged the development of a bill, BioShield I, just enacted to remedy such defects and is pushing on with a new BioShield II bill.

A second group of critics argues that the NIAID biodefence funding is part of a major overreaction to a terrorist threat that has been inflated beyond sensible limits. These critics argue that US biodefence funding, of which the NIAID is one of the major recipients, could easily be misperceived by other countries as being more offensive than defensive in nature.

What is clear is that the NIAID activities will lead to a huge increase in knowledge and understanding of these pathogens and our immune system defences against them. Much of this knowledge, which can be used for both good and ill, will come into the public domain at a time when national and international controls on the possible hostile use of biology leave much to be desired.

Introduction

Since the terrorist attacks on the United States in September 2001, and particularly the sending of anthrax-contaminated letters, the United States has vastly expanded its biodefence efforts. The US National Institute of Allergy and Infectious Diseases (NIAID) is the main institute of the National Institutes of Health for the support of biodefence research. It has, as part of the overall effort, vastly expanded, intensified and accelerated its research programme in biodefence. This report provides a summary of the aims and accomplishments of the NIAID programme and then examines criticisms of the programme being made in the ongoing debate on biodefence within the United States. The work reported here was carried out during May, June and July of 2004.

Origins of the NIAID Programme

In August 2003 NIAID published a *Summary of NIAID Accomplishments in Biodefense Research*.[1] This stated that NIAID had developed more than 50 biodefence initiatives in Fiscal Years 2002 and 2003, that about 75 per cent of these were new initiatives and that 25 per cent were expansions of existing contracts. The summary is divided into five sections on: New Initiatives; Ongoing Initiatives; Scientific Accomplishments; Clinical Evaluations of New Drugs; Diagnostics and Vaccines; and Strategic Planning. Of particular interest here is the section on Strategic Planning which sets out a series of "Blue Ribbon Panels" and Experts' Group Meetings which were convened to consider what needed to be done in specific areas of research (Table 1).

Table 1: Blue Ribbon Panels and examples of Experts' Meetings on aspects of biodefence*

	Date	*Topic*
2002	February	Highest priority areas (Category A agents)**
	June	Atopic dermatitis and vaccinia immunization
	June	Immunity and biodefence
	October	Category B and C agents**
2003	February	Medical countermeasures for radiological threats

* From reference 1
**Blue Ribbon Panels

The strategic plans that NIAID developed as a result of the Blue Ribbon Panel meetings are of especial interest. These were published as *NIAID Strategic Plan for Biodefense Research*,[2] *NIAID Biodefense Research Agenda for CDC Category A Agents*,[3] and *NIAID Biodefense Research Agenda for Category B and C Priority Pathogens*.[4] Clearly, also, the the *Summary of the NIAID Expert Panel on Immunity and Biodefense*[5] has to be taken into consideration, given the importance of the host immune responses and pathogen immune evasion mechanisms in pathogenesis. We can get an overview of what the NIAID programme is designed to do by examining these reports in turn. For the most important Category A agents, NIAID also produced a progress report in August 2003 which allows an initial assessment of how NIAID sees its own progress in achieving its targets.[6]

The scale of the problems facing NIAID can hardly be overestimated. For example, in the mid-1990s, as concerns about biowarfare and bioterrorism were renewed, the *Journal of the American Medical Association* published a special communication[7] written by members of the US Medical Research Institute of Infectious Diseases entitled "Clinical recognition and management of patients exposed to biological warfare agents." This paper reviewed existing knowledge on key threats such as anthrax, plague, smallpox, viral hemorrhagic fevers and botulism. The authors concluded, in part:

> "...The unfortunate fact remains that humans are often the most sensitive, or the only, detector of a biological attack. Without knowledge of the attack, an increasing number of patients presenting with signs and symptoms caused by the disseminated disease agent is the most likely first indicator that a BW [attack] has occurred."

Worse, they added:

> "Many, if not most, diseases caused by weaponised biological agents present with nonspecific signs and symptoms that could be misinterpreted as natural occurrences..."

So even *knowing* that an attack had taken place so that treatment plans could be put into effect was problematic in the mid-1990s, and there is little chance that this situation had changed by the time NIAID began its programme of work.

The NIAID categorisation of the threat agents is based on that developed by the Centers for Disease Control (CDC) in Atlanta. A report in 2002 summarised an effort to review the threat potential of various agents to civilian populations.[8] The assessment considered four general areas:

> "1) public health impact based on illness and death;
> 2) delivery potential to large populations based on stability of the agent, ability to mass produce and distribute a virulent agent, and potential for person-to-person transmission of the agent;
> 3) public perception as related to public fear and potential civil disruption; and
> 4) special public health preparedness needs based on stockpile requirements, enhanced surveillance, or diagnostic needs..."

Such considerations allowed the potential threat agents to be divided into Groups A, B and C, depending on "the potential for high impact," Category A agents having the "greatest potential for adverse public health impact with mass casualties." Category A agents thus include smallpox, anthrax, plague, botulism etc. whereas Category B agents include organisms that cause Q fever, brucellosis and so on. That then is the background to the NIAID consideration of its research agents: a great deal needing to be done and marked differences between the priorities needing to be given to the different threat agents.

The NIAID Programme

NIAID Strategic Plan for Biodefence Research

For the purpose of the strategic plan, NIAID defined bioterrorism[9] as "the use of microorganisms that cause human disease, or of toxins derived from them, to harm people or to elicit widespread fear or intimidation of society for political or ideological goals." It argues that the anthrax attacks had exposed "an unmet need for tests to rapidly diagnose, vaccines and immunotherapies to prevent, and drugs and biologics to cure disease caused by the agents of bioterrorism." Crucially, it noted that an important element in the overall effort to fulfil these needs was biomedical research.

The mission of NIAID is seen to be two-fold:

> "...to understand the pathogenesis of these microbes and the host response to them..."

and:

> "...to translate this knowledge into useful interventions and diagnostic tools for an effective response."

The agents believed to have the potential for use against the civilian population are viewed as having a wide range of possible characteristics (Table 2).

Table 2: Characteristics of agents *

- High morbidity and mortality
-Potential for person-to-person transmission, directly or by vector
- Low infective dose and high infectivity by aerosol, with commensurate ability to cause large outbreaks
- Ability to contaminate food and water supplies
- Lack of a specific diagnostic test and/or effective treatment
- Lack of a safe and effective vaccine
- Potential to cause anxiety in the public and in healthcare workers
- Potential to be weaponised

* From reference 2

It follows that the NIAID is not concerned just with the traditional military biological agents but has a much wider-ranging purview. Indeed, it sees genetically modified organisms as a potential threat also and its goals include dealing with such modified agents.

Whilst the strategic plan is focused on the microbes of concern, there are two other aspects of the intended programme. These are the role of host defence in combating the pathogen and essential research resources such as the construction of new biocontainment facilities in which some of the necessary work could be carried out. The

core scientific needs are thus divided into six sections in the plan: biology of the microbe; host response; vaccines; therapeutics; diagnostics; and research resources.

In regard to the **Biology of the Microbe** aspect of the plan, the research is intended to include "identifying and understanding the microbial components that define a pathogenic life cycle, transmission, virulence, and invasiveness." Genomics and proteomics are regarded as powerful new tools that can be used for these purposes. Table 3 shows the goals of this aspect of the plan.

Table 3: Goals in regard to biology of the microbe *

- Expand the focus of genomic and proteomic data collection and analysis of microbes that can be used as bioterrorist agents.
- Expand basic research opportunities on microbial physiology, ecology, molecular pathogenesis, and animal model development for Catogory A, B, C...organisms.

* From reference 2

In regard to **Host Response**, the plan argues that in order to develop effective vaccines, diagnostics and therapeutics it is critical to gain a better understanding of both innate and adaptive immunity mechanisms. The goals for this aspect of the programme are set out in Table 4.

Table 4: Goals in regard to host response *

- Expand the understanding of and ability to modify the innate and adaptive immune response to category A, B, C...organisms.
- Facilitate clinical research on human immunology that will assist in identifying targets within innate and adaptive immune pathways.

* From reference 2

The strategic plan describes **Vaccines** as one of the most successful public health measures. Clearly, if effective vaccination is available against a potential threat agent, its utility to a terrorist is much reduced. Because of the high level of concern about

smallpox and anthrax, developing and testing candidate vaccines against these pathogens is given the highest priority in the plans, as can be seen in Table 5.

Table 5: Goals in regard to vaccines *

- Develop and test vaccine candidates for civilian bioterrorism threats with an immediate emphasis on the licensure of new generation smallpox and anthrax vaccines.
- Develop cell-culture-based approaches for viral vaccine development.
- Develop improved vaccine approaches by focusing basic research interests to expand knowledge for example on potential targets for vaccine design.
- Ensure manufacturing capability for all delivery vehicles, vectors, and types of vaccine.
- Expand preclinical toxicology capability needed for vaccine development.

* From reference 2

The plan states that the development of new anti-infectives and immunotherapies and the screening of existing therapeutics to test their activities against bioterrorism agents is a high priority. Thus the goal set out under the **Therapeutics** heading is to:

> "Increase the number of licensed antimicrobials, immunotherapeutics, and antitoxins available for responding to select agents of bioterrorism through accelerated screening of new and existing agents..."

Similarly, under the **Diagnostics** heading, the goal is to:

> "Expand interest and direction in the development of highly sensitive, specific, inexpensive, and easy-to-use tools for clinical diagnosis of potential agents of bioterrorism..."

Finally, in regard to **Research Resources**, the stated aim is to:

> "Expand the development of general and specific research resources to assist in the rapid development of new tools and interventions..."

Under each of the main goals set out here the plan lists more detailed objectives for meeting the goals. For example, under research resources the goal is to be achieved, in part, by "[d]eveloping BSL-3/4 capability at Centers of Excellence for Bioterrorism and Emerging Disease Research."

This then is the overarching context within which work on specific agents was to be undertaken.

NIAID Biodefence Research Agenda for CDC Category A Agents

The NIAID research agenda for the most dangerous category A agents covers anthrax, smallpox, plague, botulism, tularemia and viral hemorrhagic fevers. The February 2002 research agenda document,[10] begins with a brief review of the six priority areas for biodefence research in the manner just described in the strategic plan. This section is followed by a set of recommendations intended to apply to all areas of NIAID counter-bioterrorism research. The recommendations are divided into sub-sets related to immediate research and to intermediate and long-term research. Some examples are shown in Table 6.

Table 6: Examples of general recommendations for all NIAID bioterrorism research *

Immediate research

-Develop regional Centers of Excellence for Bioterrrorism and Emerging Diseases Research.

-Expand non-human primate capability to evaluate new therapeutic and vaccine products.

-Expand extramural and intramural research and clinical infrastructure, including construction and renovation of BSL-3/4 laboratories.

-Encourage structural genomics and proteomics research for the targeted development of drugs, vaccines, and diagnostics.

-Enhance adjuvant discovery and rational design of *Toll* system mediators.

-Identify and characterize innate and adaptive immune responses that occur after exposure to agents of bioterrorism and enhance basic research on mucosal immunology.

Intermediate and Long-Term Research

-Examine human genetic variation in response to therapy, in drug susceptibility, and in infectivity.

-Analyse unique responses at the genome level to infection with agents of bioterrorism.

-Define the genetic basis of host susceptibility to infection with agents of bioterrorism.

-Identify pathogen-induced immunoregulatory and immunosuppressive effects that influence the host's ability to mount an effective immune response and to respond to post-exposure vaccination or immunotherapy.

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* From reference 3

If these recommendations are carefully considered - for example, the last one under Intermediate and Long-Term Research in Table 6 - it is difficult to avoid concluding that the aim is to gain a mechanistic understanding of pathogenesis and prevention in regard to these microorganisms.

For each of the biothreat agents considered in the report there is a brief review of its main characteristics, a section on each of the six priority areas and then a list of immediate and intermediate and long-term research goals for that particular organism. It is obviously impossible to review the whole range of the programme here, but some key aspects of the work on each agent can illustrate the nature of the programme intended.

Thus in the biology of the microbe part of the section on **anthrax**, it was noted that the sequencing of the *Bacillus anthracis* chromosomal genome was almost complete and the key genes contained in plasmids had already been sequenced. The NIAID intention was to proceed to expand sequencing efforts with a comprehensive genomic analysis not only of *Bacillus anthracis* but also of related bacilli. This genetic information would then "provide a framework in which to evaluate the basis for differences in pathogenicity and virulence that have been noted between strains." Furthermore, a comprehensive bioinformatics resource would be developed and would serve as a prototype for similar genomic database systems that would subsequently be developed for other bioterrorism agents.

While these long-term aims are being pursued, the key problem remains of finding a vaccine that can be safely used for the civilian population. The US Department of Defense is using Anthrax Vaccine Absorbed (AVA) but this requires six doses over a

period of 18 months - and, as the report notes, this is too long a period to deal with a bioterrorism incident, and there are concerns over the safety of the young, elderly and immunocompromised, if given this vaccine. There are drugs which may be effective against inhalation anthrax if given soon enough but the report notes the need for an approved rapid diagnostic test since "[c]ulture remains the standard confirmatory test, but definitive identification of *B. anthracis* requires additional testing beyond standard blood culture."

The section on **smallpox** notes that, because of the hazards involved, the smallpox virus has not been well studied, though the related vaccinia virus used for vaccination against smallpox has. However, as the understanding of cell-mediated immunity was in its infancy when smallpox vaccination was discontinued, there is little information on the immune response mechanisms. The vaccinia virus is very effective in preventing subsequent infection, but it is highly reactogenic and can cause severe, sometimes life-threatening, complications. So whilst the United States has good stocks of the FDA-approved Dryvax vaccine, the immediate research goals include the following, to:

> "Expand the existing supply of live and attenuated vaccines, with particular emphasis on vaccines with reduced reactogenicity."

and to:

> "Determine the correlates of immunity for smallpox vaccines through the detailed evaluation of immune responses to Dryvax vaccine."

while the intermediate and long-term research goals include these, to:

> "Develop detailed innate and adaptive immunological profiles of responses to orthopox vaccines."

and to:

> "Develop animal model capability and provide the required standardization and validation for the development of vaccines and therapeutics against smallpox."

The goals obviously place considerable emphasis on developing new antiviral drugs and, given our developing understanding of immune evasion mechanisms in these large viruses, it is not surprising that the long-term goals include:

> "Expand basic research on host-virus interactions, viral replication, and immune evasion mechanisms."

and finally:

> "Investigate the effect of infection on cytokine production."

It is clear, however, that the results of this kind of research would inevitably increase the possibility of malign application by those with hostile intent and must raise questions of oversight and data security.

Plague and other pathogenic bacteria need to remove iron from the host in order to survive. The report notes that one of the iron transport systems used by *Yersinia pestis*, the causative agent of plague, involves the synthesis of yersiniabactin (Ybt) and, since this operates in the early stages of infection, it could be an excellent target for early intervention and treatment.

Though a killed vaccine has been licensed for use in the United States for those at high risk of developing bubonic plague, the report rather dismally points out that:

> "...the vaccine did not prevent or reduce disease from pneumonic plague. The vaccine has not been produced since 1999 and is no longer available. *Clearly, we need to develop a new vaccine*..." (emphasis added)

Treatment of plague with antibiotics is generally successful, of course, but success depends on how quickly drug therapy begins, the size of the dose of inhaled bacteria and the supportive care of the patient. If treatment is delayed by more than 24 hours after symptoms begin, mortality remains high. The report notes that several drugs are recommended for treatment but argues that:

> "...the potential use of engineered, multi-drug-resistant strains as agents of bioterrorism emphasizes the need to develop alternative treatment strategies and antimicrobials with novel mechanisms of action."

Complicating the problem of the need for rapid therapeutic action is the lack of a speedy diagnostic test that is widely available. Thus it is not surprising to find the search for new vaccines, diagnostics and therapeutics emphasised in the list of research goals.

Botulinum toxin, as the report points out, is highly lethal and easily produced and released into the environment. The structure of the toxin is well understood, as is its action in preventing the fusion of acetylcholine-containing vesicles with the presynaptic membrane - particularly at neuromuscular junctions, thereby preventing transmission of nerve impulses and the functioning of muscles.

The botulinal toxins produced by *Clostridium botulinum* have seven immunological serotypes, A to G. Therapy for botulism in humans includes the use of an equine antitoxin. The licensed antitoxin has neutralising antibodies to A, B and E serotypes. An equine heptavalent antitoxin (A-G) is being developed by the Department of Defense, but there are indications of safety problems, for example for pregnant women, older people and young children.

There is no approved vaccine to prevent botulism. An investigational botulinum toxoid is available for laboratory workers, but immunity develops over months so it would not be useful for post-exposure prophylaxis. Antibiotics, of course, are not effective against a non-living toxin. More seriously, the report notes that botulism is frequently misdiagnosed. The mouse assay used to confirm clinical diagnosis is based on neutralisation by specific antibodies and can take two days. It is, moroever, only available in a few laboratories. Clearly, as the document points out:

> "...A rapid and sensitive diagnostic for botulism is essential for treatment because samples must be obtained before antitoxin treatment is begun."

It follows that the immediate research goals are directed, for example, to:

> "Process, produce, and conduct phase I and II trials with the heptavalent equine antitoxin.
>
> Scale up production and phase I testing of three human monoclonal antibodies to toxin A.
>
> Develop and test human monoclonal antibodies to toxins B, E, C, F, G and D.

Develop recombinant fragment C vaccine against toxins A, F, E, C, G and D."

and:

> "Develop rapid and inexpensive diagnostics for botulism toxins and their genes for use in multiple settings."

In the longer term, more specific interventions are indicated by the goal of being able to "[d]evelop systems for the delivery of small molecule inhibitors to cholinergic nerve cells."

Obviously, from the preceding discussion of the research agenda for the well-known agents anthrax, smallpox, plague and botulinum toxin, there were considered to be major deficiences in the available medical countermeasures. However, in regard to the less well-known - but previously weaponised - agent which causes **tularemia**, the situation described appears to be somewhat worse. The NIAID document points out, for example, that the fundamental mechanisms involved in the virulence and pathogenesis of *Francisella tularensis* are just not understood.

A live attenuated vaccine is available for laboratory workers but it is noted that:

> "...the vaccine is not effective for postexposure immunization because of the incomplete protection it affords and the short incubation time of inhaled tularemia..."

Tularemia can be treated with antibiotics, but knowledge of the best way to treat the disease is said to be limited because very few investigators are working on the disease. Moreover, there is no rapid diagnostic test available. The report states:

> "Rapid diagnostics for tularemia are not widely available, and normal microbiological tests are unlikely to result in identification..."

Given that background, it is not surprising that the research goals for tularemia are much less advanced than for the agents discussed previously. Examples which illustrate this point are shown in Table 7.

Table 7: Research goals for tularemia *

Immediate
-Conduct comparative genomic squencing of selected strains of *F. tularensis*, type A and B...and develop genetic systems to correlate differences in pathogenesis and virulence.

- Attract scientific researchers with expertise in a diversity of fields...to the study of tularemia.

-Develop rapid, inexpensive, and broad-based clinical diagnostics approaches for tularemia.

Intermediate and long-term
-Identify and characterise innate and adaptive immune responses that occur after initial exposure to *F. tularensis.*

-Identify new *F. tularensis* vaccine candidates that can prevent or modulate infection, both before and after exposure.

-Establish capacity for development, refinement, and production of candidate *F. tularensis* vaccines.

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* From reference 3

The **viral hemorrhagic fevers** (VHFs) are stated to be a threat because "with very few exceptions, no vaccines or proven treatments exist, and many of these diseases are highly fatal." It would thus appear that there is an even bigger medical countermeasures deficit for these agents than for tularemia. There are four types of VHFs and different viruses within each type. Examples are given in Table 8.

Table 8: Viral hemorrhagic fevers (VHFs) *

Arenaviruses: Argentinian, Bolivian, and Venezuelan hemorrhagic fevers, Lassa fever.

Bunyaviruses: Crimean-Congo hemorrhagic fever, Rift Valley fever, and Hantavirus infection.

Filoviruses: Ebola and Marburg hemorrhagic fevers.

Hemorrhagic flaviviruses: Yellow fever, Dengue hemorrhagic fever, Kyasanur Forest fever, and Omsk hemorrhagic fever.

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* From reference 3

The report notes that the life-cycles of these viruses are multifaceted, often with one or more amplifying hosts and, frequently, an arthropod (tick or mosquito) vector. No vaccines exist for VHFs except for the well-known licensed vaccine for yellow fever. Though progress is being made on a potential Ebola vaccine, even for this - the best characterised filovirus - relatively little is known about the human immune response. Generally, the only treatment for VHFs is supportive care, and clinical diagnosis is difficult because the initial symptoms are non-specific. There are tests that can be used to confirm some infections - for example, Ebola - within days of onset of the disease but work with infective strains of VHFs is clearly difficult as it has to be done in BSL-3/4 facilities.

Against that background, the research goals for VHFs involve a long list of frequently basic scientific objectives, some examples of which are shown in Table 9.

Table 9: Research goals for VHFs *

Immediate
-Develop animal models that mimic human disease for studying VHF pathogenesis in humans.
-Establish capacity for the development, refinement, and production of pilot lots of candidate vaccines for VHFs.
-Complete the genomic sequencing of representative members and strains of the VHFs, and compare them to detect differences in pathogenesis and virulence.
Intermediate and long-term
-Establish partnerships as appropriate to expand the study of the ecology of VHFs in their natural environment.
-Expand the knowledge of host and vector factors and viral proteins that contribute to the pathogenesis and transmission of VHFs.
-Identify targets within the innate and adaptive pathways that may be used to modulate infection.

* From reference 3

NIAID Biodefence Research Agenda for Category B and C Priority Pathogens

The NIAID research agenda for the less dangerous Category B and C agents was the outcome of a Blue Ribbon Panel held in October 2002. The January 2003 document[11] notes in the Preface that the panel was asked to provide advice on:

- the state of current NIAID research on the development of measures to counter the health consequences of bioterrorism using these agents;
- research goals for the highest priority areas;
- the role of the NIAID in achieving these priority goals; and
- the current list of NIAID Category B and C agents.

A footnote to the Preface points out that whilst the NIAID list of these agents closely follows that of the CDC, "the NIAID list highlights specific pathogens identified as priorities for additional research efforts as part of the NIAID biodefense research agenda." The NIAID and CDC lists are then detailed in two appendices.

The introduction to the document notes that because of the diversity of the organisms in these lists, the report is divided along different lines from the standard CDC list with the pathogens and toxins listed in different broad groups. The chapter headings appear in Table 10. Prior to dealing with these groups, the report again briefly reviews the six areas of research emphasis and the overall general recommendations for biodefense research.

Table 10: Groupings for Category B and C Agents *

- Inhalation bacteria

- Arthopod-borne viruses

- Toxins

- Food- and water-borne pathogens
  - -Bacteria
  - -Viruses
  - -Protozoa

- Emerging infectious diseases

-Influenza
-Multi-drug-resistant tuberculosis

- Additional biodefense considerations
-Recommendations on the NIAID Priority Pathogens list
-Role of industry in the Biodefense Research Agenda
-Genetically modified organisms

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* From reference 4

These recommendations are additional to the general recommendations set out in the agenda for Category A agents and are listed under three headings: Research; Product Development; and Research Resources, rather than Immediate and Intermediate and Long-Term Research. This presumably indicates an evolution towards product production and the longer-term underpinning of research through resource development. It is not the intention here to go into details of the research agenda set out for these groups of agents, but to highlight some of the key current deficiencies noted in the report.

The **inhalation bacteria** include *Brucella* species which cause brucellosis, *Burkholderia pseudomallei* (melioidosis), *Burkholderia mallei* (glanders), *Coxiella burnetii* (Q-fever), and *Rickettsia* species such as *R. prowazekii* (typhus). These organisms usually cause zoonotic diseases in other mammals but can be transmitted to humans in various ways. They are also all believed to be capable of causing infection following inhalation of small numbers of bacteria and are of especial concern because they may be weaponised in an aerosol. The diseases caused by these organisms range from the incapacitating (with low mortality) exemplified by brucellosis and Q-fever through to the highly lethal such as melioidosis, glanders and typhus.

The genomic sequences of strains of many of these pathogens had been completed, or were nearing completion, at the time of publication. However, some of the molecular mechanisms underlying virulence were little or only partially known. For example, for glanders and melioidosis it is noted that ”[v]ery little is known about the molecular mechanisms underlying *Burkholderia* virulence” and, more generally, that “[h]ost immune responses to many of the inhalation bacterial pathogens in Category B are not well understood.”

As far as medical countermeasures go, vaccination protection is largely unavailable, the report stating, “[s]afe, efficacious human vaccines do not exist for most

of the category B inhalation bacteria." The typhus vaccine used for US soldiers during the Second World War is no longer available, and the Australian Q-fever vaccine was not licensed for use in the United States. Antibiotics are effective, but treatment for some diseases can be protracted and there are fears of antibiotic resistance developing in some natural strains. Adding to the difficulties, symptoms of acute infections with these organisms are non-specific and resemble those of many other flu-like illnesses and also, rapid diagnostic tests are not available for most of these bacteria. Standardised animal models exist for these zoonotic bacteria but most require BSL3 biocontainment for propagation and animal work.

Under the section on **arthropod-borne viruses** (arboviruses) the document lists three groups as shown in Table 11. Somewhat confusingly, some of these viruses, for example CCHF and YF, were also discussed in the earlier documentation on Category A agents.

Table 11: Arthropod-borne viruses *

- *Alphaviruses*: Venezuelan equine encephalitis (VEE) virus, eastern equine encephalitis (EEE) virus, and western equine encephalitis (WEE) virus.
- *Flaviviruses*: West Nile virus (WNV), Japanese encephaliitis (JE) virus, Kyasanur Forest disease (KFD) virus, tick-borne encephalitis (TBE) virus complex, and yellow fever (YF) virus.
- *Bunyaviruses*: California encephalitis (CE) virus, La Crosse (LAC) virus, Crimean-Congo hemorrhagic fever (CCHF) virus.

* From reference 4

These viruses are regarded as a major threat because of their extreme infectivity following exposure of the victim to aerosol, and additionally because there are few vaccines or specific therapeutics that are effective against them. Additional problems are that relatively little is known about the mechanisms of pathogenesis and the infections usually cause non-specific flu-like symptoms. Furthermore, research work with CCHF and TBE requries BSL4 biocontainment while BSL3 or higher is required to work with EEE, VEE, WNV and YF.

On the other hand, the report notes that the Category B and C arboviruses discussed in this section all have enveloped RNA genomes that replicate in the cytoplasm of infected cells, outside of the nucleus. Genomic sequencing and other studies have demonstrated relationships between some of the viruses, and identified sites on genes, and proteins, that are related to virulence and its attenuation. X-ray crystallography of some alphavirus and flavivirus structural proteins is also providing insights that could lead to targets for antiviral drugs.

At the time of the report limited quantities of vaccines against VEE, EEE and WEE were available from the US Department of Defense under its Investigational New Drug programme. The vaccines, however, are far from satisfactory, with the live attenuated VEE vaccine causing 20 per cent of participants in clinical studies to fail to mount a response and another 20 per cent to develop clinical signs of disease. Live attenuated vaccines are obviously available for yellow fever, and vaccines are produced in the Far East for Japanese encephalitis. Limited quantities of two licensed vaccines are also available for tick-borne encephalitis, for use in Europe and former Soviet Union countries. Progress is being made on vaccines for West Nile virus, but no licensed vaccines are available for the CE, LAC or CCHF bunyaviruses.

The document notes that the **Category B toxins** include ricin from *Ricinus communis*, epsilon toxin of *Clostridium perfringens* and Staphylococcal enterotoxin B (SEB). Whilst not put on the list of Category A agents like *Clostridium botulinum* toxin, these are potent agents that could be used for food and water contamination as well as for an inhalation attack via an aerosol. Ricin can be produced in large quantities at low cost from the castor oil plant. It works by inactivating ribosomal protein production in the cell. *Clostridium perfringens* is an anaerobic bacterium found in the soil. The bacterium exists in five types (A-E) that between them produce seven minor toxins and four major lethal toxins. The alpha toxin is associated with gas gangrene while the epsilon toxin attacks the nervous system of infected animals. SEB is one of at least thirteen distinct enterotoxins produced by strains of *Staphylococcus aureus*. SEB is viewed as a superantigen which causes a massive over-response in the immune system. Whilst high doses of SEB can kill, lower inhaled doses lead to a severe temporary incapacitation.

A good deal is known about the mechanism of action of these toxins but the report notes that although, at the time of publication, candidate vaccines were under development and large numbers of potential drugs were being screened, for example against ricin:

> "No licensed vaccines against ricin toxin, *C. perfringens* epsilon toxin or SEB are available for humans..."

and:

> "No specific therapy exists for ricin toxin, *C. perfringens* epsilon toxin, or SEB..."

The well-documented, deliberately caused, outbreak of salmonellosis in Oregon in 1984 is used to point out the dangers of an attack using **food- and water-borne bacteria**. There are, of course, many possible agents in this group. Amongst others, the report lists "diarrheagenic *Escherichia coli*, pathogenic *Vibrio* spp., *Shigella* spp., *Listeria monocytogenes*." It also points out that as there are sporadic natural outbreaks of these diseases in the United States, it could be difficult to identify a deliberate outbreak rapidly.

Two of these pathogens are regarded as particularly dangerous threats because they can cause severe - sometimes fatal - disease, they can infect by ingestion of just a few bacilli, and they can spread by person-to-person contact. These two potential bioterror agents are Shiga toxin-producing *Escherichia coli* (STEC) *and Shigella dysenteriae 1* (Shiga bacillus). The report notes that, "[e]ach of these pathogens has been responsible for large-scale epidemics. *S. dysenteriae 1* is one of the few bacterial pathogens capable of producing a pandemic outbreak."

A good deal is known about the biology of these microbes, particularly as the genomes of many have been sequenced. Virulence genes exist on chromosomes and on mobile elements such as plasmids within the cell. New strains evolve continuously as there is a great deal of gene transfer amongst these organisms, and there is considerable concern in the United States about the emergence of antibiotic-resistant strains.

The report summarises the present situation regarding vaccines simply:

> "Few licensed vaccines exist for Category B food-and-water-borne bacterial pathogens. Available vaccines have differing efficacy and their use within the U.S. is limited primarily to individuals travelling in endemic areas..."

So vaccines against *Salmonella typhi* are restricted to preventing typhoid fever amongst military personnel and the like. And the report notes that "[t]here are currently no licensed human vaccines available for *E. coli*" and "[n]o licensed vaccines are currently available for *Shigella*." The same applies to *Clostridium jejuni*, *Listeria monocytogenes* and *Yersinia enterocolitica*. In addition to antibiotic resistance being a problem for treatment, it is difficult to be sure of the causative agent from clinical symptoms alone. Microbial culture is required which takes time. Given the possibility of resistance, antimicrobial sensitivity testing is also necessary.

Hepatitis A virus (HAV) and the caliciviruses such as Norwalk and Hawaii etc. are included in the **food-and-water-borne viruses** group. They are regarded as potential bioterrorism threats because of their high infectivity, morbidity and possible rapid and widespread dissemination. The genomes of HAV and Norwalk (and other caliciviruses) have been sequenced. Two vaccines for HAV are licensed in the US and others are available around the world, but the costs presently prevent universal vaccination. No licensed vaccines are available for caliciviruses. No specific therapies are available either and research is hampered by HAV being difficult to culture while "Norwalk and other caliciviruses cannot be cultured."

The report states that the most important **protozoans** in regard to bioterrorism include *Cryptosporidium parvum*, *Entamoeba histolytica*, and *Toxoplasma gondii*. It notes that these organisms can infect large numbers of people via food- and water-borne contamination and some subsequently through person-to-person contact. It also suggests that "most can be genetically manipulated to increase virulence or resistance to anti-infectives." The basic mechanisms of pathogenesis are little understood and culture techniques and animal models to facilitate vaccine research are lacking.

Amongst **emerging infectious diseases** influenza is appropriately picked out, with the report noting, for example, that:

> "The characteristic epidemic and pandemic patterns of influenza A infection are a result of antigenic drift and antigenic shift, respectively....The possibility that

> purposeful manipulation of influenza A genes can be used to create an influenza virus with a novel HA subtype makes influenza A relevant to biowarfare concerns."

Similarly, multi-drug-resistant tuberculosis is seen as an emerging threat, and whilst there is a licensed vaccine (BCG), it is not recommended for use as it is highly variable in its efficacy in preventing pulmonary TB.

In regard to the **additional biodefense considerations**, the report recommends adding several new agents, and categories of agents, to the B list. Concerns are expressed about the difficulties of moving from research to production of licensed vaccines, and the dangers of genetic manipulation of threat agents is stressed.

NIAID Expert Panel on Immunity and Biodefence

The summary of the expert panel meeting on immunity and biodefence held in June 2002[12] is much briefer than the preceding reports. It notes:

> "...Panel members identified high priority research areas in immunology that would lead to improved biodefense strategies, and recommended methods by which these research goals might be achieved..."

The summary is set out in five sections (Table 12).

Table 12: Structure of the summary of the Expert Panel on Immunity and Biodefense *

AREAS OF RESEARCH
- *Innate immune mechanisms*
  - Adjuvants for vaccines
  - Short-term protection
- *Adaptive immune mechanisms*
  - T and B effector cells
  - T and B cell memory
  - Epitope identification
- *Human immunology*
- *Immunity for infants, the elderly and the immunocompromised*

RESEARCH RESOURCE NEEDS

INDUSTRY INVOLVEMENT

RESEARCH TRAINING PROGRAMS

* From reference 12

The summary has an optimistic tone, suggesting that recent advances, for example in the understanding of innate immunity, has laid the foundations for practical measures both in traditional methods of protection with vaccines and adjuvants and by novel means. However, the report is full of statements that stress the current lack of understanding of crucial issues, for example:

> "Characterization of the innate immune responses to specific pathogens is also an important area of research, *because little is known for most of the CDC/NIAID Category A-C pathogens*..." (emphasis added)

and:

> "...Again little is known about immune memory, especially in the human, and considerable basic research is needed to identify the most effective memory cell subsets and their mechanisms of regulation..."

and:

> "...Very few epitopes have been described for Category A-C pathogens..."

and:

> "The immunological status of the human population is highly variable....Little is known about the fundamental differences known to exist between the healthy adult immune system and the immune system in early development or in senescence..."

Little wonder, then, that the panel made strong recommendations on facilitating human immunological research relevant to biodefence, the establishment of core resource facilities and so on.

Assessments of the NIAID Programme

Now, in mid-2004, it is possible to begin to assess the impact of this major programme. A starting point is the NIAID report on progress on Category A agents produced in August, 2003.

NIAID Biodefence Research Agenda for CDC Category A Agents: Progress Report

In August 2003 NIAID produced a progress report on its work on the CDC Category A Agents anthrax, smallpox, plague, botulism, tularemia, and viral hemorrhagic fevers. The report has a final section on Immunity and Biodefense and begins with a section on Progress on General Recommendations of the Blue Ribbon Panel.[13] The progress described in the report is that related to the immediate goals of the research agenda for Category A agents.[14] With respect to the recommendation on developing regional centres of excellence against bioterrorism, it notes:

> "...NIAID expects to award 7-8 centers in late FY 2003. A planning grant component was included in this initiative, and NIAID expects to award 2-3 planning grants in late FY 2003."

Such grants were subsequently awarded.[15,16]

Concerning progress on reaching the immediate goals set for work on the agents, a series of specific research achievements is given for each of these pathogens (Table 13).

Table 13: Scientific progress in research on CDC Category A Agents*

ANTHRAX	
	- Key features in the pathogenesis of anthrax identified: research may yield an antitoxin
	- Molecular mechanisms by which anthrax evades immune systems uncovered
	- Researchers unravel anthrax genomes
SMALLPOX	
	- Understanding of pox virus pathogenesis has improved
	- Immune response to vaccinia virus has been further characterised
	- Existing supply of smallpox vaccine can be expanded to protect more Americans
	- Pill form of cidofovir developed for treatment of smallpox
PLAGUE	

- Genome sequence for the organism that causes bubonic and pneumonic plague has been completed
- Single gene change led to deadly plague organism
- Genes in the yersiniabactin iron transport system have been identified

BOTULISM

- Sequencing of the *C. botulinum* Hall strain A bacterium genome has been completed
- Research provides a better understanding of botulinum toxin entry into cells
- Animals are protected after immunisation with A and F toxins

TULAREMIA

- Host defense mechanisms revealed in mouse model
- Conjugating the O-polysaccharide of the lipopolysaccharide (LPS) of *Francisella tularensis* to bovine serum albumin (BSA) does not change the vaccine's effectiveness

VIRAL HEMORRHAGIC FEVERS

- Accelerated vaccine for Ebola protects monkeys
- Methods developed to study individual proteins from these viruses in regular, low containment laboratories
- Development of a novel assay for the detection of human antibodies to Ebola using reverse genetic systems
- Novel mechanisms of antibody-dependent enhancement discovered for Ebola

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* From reference 6

More generally, the report emphasises the considerable progress made in regard to each agent (Table 14).

Table 14: Statement on progress in regard to Category A agents*

Anthrax

"...significant progress has been made in understanding the basic mechanisms by which *B. anthracis* causes disease, and in developing countermeasures against anthrax..."

Smallpox

"...significant progress has been made in understanding the variola virus and how it causes disease, and in developing countermeasures against its intentional release..."

Plague

"...significant progress has been made in understanding *Y. pestis* and how it causes disease, and in developing countermeasures..."

Botulism

"...significant progress has been made in understanding *C. botulinum* neurotoxins and how they cause disease, and in developing countermeasures to protect exposed individuals..."

Tularemia

"...progress has been made in understanding *F. tularensis* and how it causes disease, and in developing countermeasures against its intentional release..."

Viral hemorrhagic fevers

"...significant progress has been made in understanding how the organisms responsible for VHFs cause disease, and in developing countermeasures against their intentional release..."

---

* From reference 6

This somewhat suspicious repetitive recording of progress, as we shall see, was not accepted by all observers in the United States.

The Critics: 1. An Insufficient Response to the Threat

A US DoD Defense Science Board Summer Study in 2000 analysed the current and future state of diagnostics, vaccines and therapeutics for 19 agents considered to be major threats.[17] The results of this study can be easily summarised and make grim reading. For 19 agents and 3 categories of countermeasures a total of 57 countermeasures would be needed. In 2000, the report suggested, *one* was available, in five years there would be 20 and in ten years 34. For the military, of course, vaccination is the key measure as effective vaccination for limited numbers of troops is feasible logistically and allows them to fight on without requiring huge medical support. But as a recent report on countermeasures pointed out:[18]

> "At the time of the [1991] Gulf War, only one medical countermeasure approved by the Food and Drug Administration (FDA) - the vaccine against anthrax - was available to the Department of Defense (DoD) to protect troops against possible biological warfare agents. In 2003, despite congressional attention and good-faith efforts on the part of the DoD scientists, no new vaccines against biowarfare agents are available to service members."

The report went on to examine in detail the difficulties for the Department of Defense in developing and producing new vaccines.

For protection of the civilian population also, preventive vaccination, diagnostics and therapeutics are all required but the situation in regard to approved countermeasures for *civilian*s is equally limited. A combination of information from numerous sources was recently provided for Category A agents by Smith *et al.*[19] Their summary table is reproduced in Table 15.

Table 15: FDA-approved medical countermeasures for Category A bioweapons threats*

Category A disease	*Vaccine*[a]	*Post-exposure Therapy*[a]	*Rapid Diagnostics*[a]
Anthrax	Yes	Yes[b]	No
Smallpox	Yes	No	No
Plague	No	Yes[b]	No
Botulism	No	Yes[c]	No
Tularemia	No	Yes[b]	No
VHFs[d]	No[e]	No[e]	No

a Only FDA-approved vaccines, therapies, and rapid diagnostics are considered.

b There are limited numbers of antibiotics specifically FDA-approved for these diseases. The knowledge required to create antibiotic-resistant strains is in the open literature.

c Antitoxins can be effective therapies for botulism, but they must be used early - they can only stop progession of paralysis, not reverse it. Antitoxins are in very limited supply.

d VHFs = Viral hemorrhagic fevers.

e A few members of this large family of viruses do have FDA-approved therapies and vaccines.

* Table from reference 19

Correcting this situation will not be a simple matter despite the money that has been and will be spent by NIAID.

First, as many commentators have noted and as Smith *et al*. detail:[19]

> "NIH [National Institutes of Health] has had considerable success in promoting and funding basic biomedical research, but it has very little experience in the complex process of transforming such knowledge into licensed drugs or vaccines..."

and whilst NIAID leaders have stated that they intend to take on the new role in regard to biodefence, it has been asked seriously whether that is really compatible with NIH's historic mission of basic biomedical research.[20] Indeed, there appears to be a broad consensus in the United States that in order to solve the problem, it will be necessary to engage the biotechnology and pharmaceutical industries in order to effectively develop and produce the necessary countermeasures.

This job of linking the government-funded basic research with the industrial world will be difficult because of the incompatibility of the communities in ethos, aims and methods of working. Both the biotechnology and pharmaceutical industries are involved in high-risk, but potentially high-profit ventures. Biotechnology companies tend to be small and engaged in a fast-paced attempt to get a single product to the stage where it is taken up by a pharmaceutical giant. These companies have been in difficulties in the recent economic slowdown and may not be attracted to the constraints of government funding, apart from ensuring survival. The pharmaceutical giants possess the knowledge of how to invest large sums to bring products to market, but they may not see biodefence countermeasures as ensuring the high profits they expect from their successful ventures. Moreover, they have expressed concern about liability protection if they *do* engage in the production of "drugs and vaccines that cannot ethically be tested for efficacy in human clinical trials." Clearly, many biodefence countermeasures may only be tested in animal models until they are required to answer an emergency and are given to large populations of people.

In order to deal with such problems, in May 2004 the Senate passed the Project Bioshield Act. An editorial in the *Washington Post*[21] reported that the act:

> "...provides $5.6 billion in funding over the next decade for purchasing vaccines and other medicines..."

and stated:

> "...It also streamlines research procedures and in a national emergency allows the government to distribute treatments that have not been approved by the Food and Drug Administration."

So far, so good then, but the editorial went on to note that, of the 57 countermeasures the Defense Science Board saw as necessary, only two were available. Many concerns remained for the industry, for example:

> "...Critics of the new bill note that its liability protections for companies whose products are used without FDA approval are weak..."

and:

> "The drug and biotech industries worry that purchase price issues remain fuzzy and intellectual property protections are not ironclad. Too many remember the pressure put on Bayer, the producer of the anthrax drug Cipro, to cut prices dramatically following the 2001 anthrax attacks..."

Little wonder then that, although the Bioshield proposal was also passed by the House in mid-July and signed into law by the President, Senators Lieberman and Hatch have already begun work on a new bill (Bioshield II) to make a larger, longer-term and more systematic approach to the problem.

The critics of the present situation and approach have an additional deeper concern. They maintain that it is totally inadequate to focus just on countermeasures for known agents when there is very clear evidence that novel agents may have to be dealt with in the aftermath of an attack on the United States. Terming the agents known today "20th century bioweapons," Smith *et al*. argue that:[22]

> "Growing numbers of people in the scientific community now recognise that looming just ahead is a far more daunting array of potential engineered bioweapons agents..."

They call such agents "21st century bioweapons." The "looming threat" was the subject of an article which considered what the Soviet Union's illegal late Cold War programme can tell us about what such future weapons might include.[23] The article argued in part:

> "...Many politicians likely knew that conservative estimates put the number of potential bioterror agents at 70 to 80 not merely 19. For genetically engineered pathogens, the possibilities are wide open..."

and it pointed out some known projects of the Soviet offensive programme:

> "Hunter's role is fairly clear: it systematically combined different viruses' genomes to engineer novel pathogens with exotic killing properties. Flute focused on psychotropic and neurotropic agents..."

The article ended very pessimistically by practically dismissing the possibility of defending the civilian population:

> "...Project Bioshield, as currently formulated, is a placebo with which Washington policymakers hope to quiet the public. Its premises are weak and insubstantial. The U.S. population *cannot* be "hardened" against biological attack. Emerging technologies, such as biosensor devices, are largely experimental. Vaccines will *not* be forthcoming from big pharmaceutical companies. A good defense against bioweapons has not yet been proposed..."

Policymakers have also argued that the present policies are aimed at a static threat and will not cope with the dynamic evolving threat made possible by modern biotechnology.[24] Perhaps the fullest account of the possibilities has been given by Petro *et al*.[25] Taking a long view, they argue that since there are only a certain number of biological agents suitable for use in an attack, the defence will eventually be able to deal with them. This will force the offense to move to modify the agents - for example by introducing antibiotic resistance. However, there are only a certain number of possible modifications so, again, the defence will eventually be able to catch up. As our understanding improves, the offense will be able to turn its attention away from the agent towards the physiological process it wishes to manipulate. There is a multitude of potential physiological targets and ways to manipulate them and so it seems unlikely, in the end, that the defence will be able to counter such a diverse offensive potential.

The Critics: 2. A Potentially Dangerous Overreaction

Rather than seeing the NIAID programme as an inadeqate response to the threat, other commentators have worried that it could be an overreaction. The question has been raised as to whether the terrorist threat from biological weapons has escalated so much since 2001 that this kind of response is required.[26] Others have expressed concern that, given the wider context of American rejection of the Biological and Toxin Weapons Convention (BTWC) Protocol,[27] and the exposure of their dubious undeclared biodefence activities,[28] there could be a grave danger of the work being misperceived by other states

as part of an offensive rather than defensive programme. This concern increased when it became known that the NIAID work could be linked to that of the new National Biodefense Analysis and Countermeasures Center (NBACC) at Fort Detrick, Maryland. A briefing by Lieutenant Colonel George Korch, Deputy Director, given early in 2004, clearly shows the Department of Health and Human Services and NIAID being linked to the NBACC. Particular concern has been caused by the intended "Threat Analysis" to be undertaken by one of the four NBACC centres. This Biothreat Characterization Center will, for example, carry out "Red Teaming" of threat scenarios, and biothreat analysis is to involve "Acquire, Grow, Modify, Store, Stabilize, Package, Disperse [agents]." The head of the US delegation which negotiated the BTWC was among the distinguished authors[29] who argued that:

> "...Taken together, many of the activities detailed...may constitute *development* in the guise of threat assessment, and they certainly will be interpreted that way..."

Development is specifically prohibited by the BTWC so such charges are important. There is clearly a danger is such circumstances that other states will follow the US lead and create an arms race in biological offense and defence.[30]

What Happens to the NIAID Programme Now?

In late April 2004 the White House issued a Department of Health and Human Services (HHS) fact sheet on biodefence preparedness.[31] This began by noting that biodefence spending had increased by a factor of 17 and that another significant increase was proposed by the Administration for next year (Table 16).

Table 16: Federal investment in biodefence*

FY 2001	-	$294 million	[HHS budget]
FY 2002	-	$3 billion	[HHS budget]
FY 2003	-	$4.4 billion	[combined HHS and DHS budgets for biodefense]
FY 2004	-	$5.2 billion	[combined HHS/DHS - including BioShield proposal]

* From reference 31

The fact sheet went on to detail progress in a number of sections. These included: *The Biodefense research initiative is the largest single increase in resources for any initiative in the history of NIH*; *Progress in Biodefense research has been swift and substantial*; and *Capacity is being expanded to produce medical countermeasures to protect Americans from bioterrorism attacks*. At the same time, another publication from the White House[32] reviewed what had been achieved and stated that, building on such accomplishments, a comprehensive evaluation of capabilities and priorities for further action had been carried out. This had resulted in a blueprint for the future defence programme entitled *Biodefense for the 21st Century*.[33]

On 3 June 2004, giving evidence to Congress on the National Biodefense Strategy, Anthony Fauci, Director of NIAID,[34] stressed that:

> "The ultimate goal of all NIH biodefense research is the creation of new and effective medical countermeasures, including vaccines, therapeutics and diagnostics against potential bioterror agents..."

and then that the NIH as the lead agency is carrying out such government-sponsored research. He also pointed out that, within NIH, NIAID is responsible for the bulk of this research and that work is co-ordinated through the NIH Biodefense Research Coordination Committee which he chairs. NIH is part of the Department of Health and Human Services, (HHS) and within HHS biodefense work is co-ordinated with other agencies such as CDC (Centers of Disease Control by the office of the Assistant Secretary for Public Health Emergency Preparedness. Additionally, NIAID staff meet regularly with agencies of the Department of Defense and at the highest level co-ordination of biodefence research is carried out by the White House, particularly the Homeland Security Council and the National Security Council. Critics still view this degree of organisation as inadequate to provide the required drive and direction,[35] but it is quite clear that the NIAID research programme will continue for some years into the future.

Key questions remain to be answered in those future years. What is the programme likely to achieve? When will the required countermeasures be forthcoming?

And if NIAID proves incapable of producing them, what will Congress, or the next Administration, do then? Last, and by no means least, what will the reaction be in other countries - both friendly and not so friendly? One thing is certain, given the level of funding available[36] - vast quantities of new scientific knowledge and new technologies will be generated. Much of the new information will come into the public domain and will be essentially dual-use - usable both by those with benign and with malign intent. And all of this will happen over the coming years in the absence of effective national and international controls over the use of this new knowledge.

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