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Review

Overview: cause and prevention in biowarfare and bioterrorism

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Abstract

Bioweaponry is rooted in the ancient past. It became a science in the early 20th century following the breakthrough discoveries in microbiology and immunology of the late 1800s. The 20th century, with its major and minor wars, saw the research and development of biological weapons capable of immense destruction of life, which were used both by nations in preparation for military warfare and by individuals who engage in asymmetric warfare. Treaties, international agreements, and political pursuits have not been able either to control or to rid the world of bioweapons. The *tools* for specific defense against bioweapons consist of vaccines against both viruses and bacteria, and of antibiotics and drugs against bacteria. Vaccines and antimicrobials are of limited usefulness because of the large number of possible microbes that can be used for weapons, because of antimicrobial resistance to drugs and antibiotics, and because of limitations in technical feasibility for developing vaccines and antibacterials against certain of the agents. Induction of non-specific innate immunity by immunostimulatory vaccines (at one time licensed) needs to be explored for possible immunoprophylactic–therapeutic activity when administered immediately following exposure to bioweapon pathogens. The ideal *solution* to the bioweapons problem lies in measures to end their development and application throughout the world. Emphasis was made at the recent World Economic Forum of the need to end poverty and hunger in the world as a means to reduce the incentive to engage in warfare. Added to this is betterment of health, focused mainly on preventable diseases. A further solution to the problem may lie in the development of modern *robotic systems* for rapid forensic detection of development and production of bioweapons by "rogue" nations and even by individuals.

This review deals with the specifics of the development of bioweapons and their control by vaccines, by therapy with antibacterials, by non-specific immunostimulants, by advanced systems for detection of development and deployment of biological agents of destruction, and by political and health-giving initiatives.

Keywords: Biological weapons; Bioterrorism; Disease prevention; Disease treatment

1. Introduction

In its simplest sense, direction of bioweapons against the military is biowarfare. Direction against civilians is bioterrorism. The scientific community in the US is expected increasingly to provide answers to problems for which political and diplomatic processes fail to give satisfactory resolution. In many respects scientists should be so engaged because it was the practice of science itself which created the tools for chemical, nuclear, and biological warfare. Scientific pursuits which are typically directed to benefit mankind, are sometimes subverted to destructive purpose by the political process.

The battle against bioweapons is an engagement of biological sciences to provide means to detect and avert agents of destruction, and to prevent and treat diseases of intent. The task is technically difficult and, like research in offense, is often conducted in secrecy.

2. Historic overview of biological warfare, treaties, violations, and compliances

2.1. Early biowarfare

There has been persistent interest (Table 1) throughout history in use of biological means to destroy the enemy during warfare [1–3]. In primitive times, poisoning and fecal contamination of arrows, spears, and pungi sticks were commonly used. During ensuing centuries, contamination of water and food supplies, projection of plague-infected cadavers into enemy camps, and release of infected animal vectors were employed. Distribution of infected fomites by colonial powers to reduce native populations has been recorded [1].

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Table 1
Biological weapons from ancient times through World War I

Primitive times
Poisoning or fecal contamination of arrows, spears, and pungi sticks
Nineteenth century and before
Contamination of water supplies
Projection of infected animal and human cadavers into enemy camps
Release of infected animal vectors such as rats
Distribution of infected fomites such as blankets and handkerchiefs
Twentieth century—application of new science born in the late 1800s
World War I
Built largely on the creation of the science of microbiology mainly in Germany and France in the late 1800s
Most prominent, German infection of livestock and feed supplies

2.2. World War I and beyond

Biological warfare became a science during World War I. It was built on the previous creation of the science of microbiology, principally by Robert Koch in Germany and by Louis Pasteur in France during the late 19th century. The most prominent application of weaponry during the war was by Germany in its infection of livestock and animal feed supplies, but with no attack on people.

Following World War I, the Geneva Protocol [2] (Table 2), an international treaty, was promulgated by the League of Nations in 1925 which prohibited the use of chemical and biological weapons in warfare but with no prohibition for their development or their stockpiling. Even though there were many national signatories of the Protocol, several nations [2] listed in Table 2 entered into bioweapons research and development. Some were likely for defense alone. Particularly notable was the Japanese initiative which began in 1932 and which made extensive use of bioweaponry during its campaign against China. Procedures such as contamination of water and food supplies, release of plague-infected fleas, and delivery of infectious agents by aircraft were employed.

Table 2
Weakness of the Geneva Protocol, 1925 led to bioweapons research and development by several nations

Geneva Protocol, 1925 prohibited use of chemical and biological weapons in warfare, but did not prohibit future development and stockpiling of bioweapons	
Weakness of the protocol led to bioweapons research and development[a] by:	
France	1922–1928, 1934–1940 (restricted)[b]
USSR	1926–?
Japan	1932–1945
Italy	1934–(restricted)[b]
Hungary	1936–?
UK	1936–?
Canada	1938–?
Germany	1940–(defensive only)[b]
US	1943–1969

Source: [2].
[a] Possibly some were for defense only.
[b] Did not engage in BW training or fielding.

2.3. World War II

With the onset in 1939 of World War II, bioweapons research achieved the level of high science with state of the art sophistication. Principals engaged in significant research [2] during World War II are listed in Table 3. The largest engagements were by Japan, the USSR and the US. Reliable information as to what was actually carried out during World War II is scant and is based on inadequate intelligence reports. The Japanese effort was a continuation of what began in 1932. According to recorded information, the initiative was probably huge, and involved delivery of plague, typhoid, cholera, anthrax and other pathogens into China by direct pollution, aerial bombs and infected vectors. Deaths were estimated but not documented [2] to be from 1000 to 222,000 persons in individual attacks. Captives who were killed by experimental work were estimated to number between 5000 and 10,000. Precise knowledge of what happened in the Japanese campaigns during World War II was lost because of a tradeoff in which war crime charges were canceled in return for release of pathology data collected in the Japanese medical experiments [2].

The US was a late entrant into biological weapons research, as recorded in "Biological Warfare: Report to the Secretary of War by George W. Merck, Special Consultant on Biological Warfare," released in 1946. This hitherto secret document was published in *Military Surgeon* in 1946 [4]. The Camp Detrick Research and Development Facility in Frederick, MD began construction in 1943 under the Chemical Warfare Service. The numbers of persons engaged grew to more than 3000 by mid 1944, with primary emphasis on defense. As stated in the Merck

Table 3
Biological weapons research during World War II

Nation	Numbers of workers (estimated)	Focus
Germany	Est. 100–200[a]	Offense research forbidden
Canada	Est. small[a]	Animal and crop diseases Rinderpest, anthrax
UK	40–50 at peak	Animal and crop diseases Foot-and-mouth disease, anthrax
Japan	Several thousand	Extensive; official information suppressed by a treaty with the US in which all charges for war crimes were dropped
USSR	Est. Several hundred[a]	Typhus, plague
US	1500–3000+	Chemical herbicides, anthrax Started too late to be important

Source: [2].
[a] Est. = estimated.

Table 4
Reported bioweapons programs post World War II

Country	Time	No. of personnel	No. of major facilities	No. of agents weaponized	Stockpiled	Used
UK	1945–1972	?	1	0	No	No
US	1945–1969/1972	3400	3	10	Yes	No
USSR	1945/1993 (?)	~60000	~35	10–12 (?)	Yes	?
Iraq	1975–present (?)	~300	7	5	Yes	No
South Africa	1981–1993	6–10	1 or 2	0	No	Yes

Source: [2].

report [4], many different studies were carried out on pathogen production, on pathogen dose and stabilization, on co-agent virulence-enhancing substances, on toxin purification, on immune response, on animal models, and on plant-destructive agents. The most important breakthrough, by the end of the war in the fall of 1945, was the development of means for small particle size aerosol delivery of both wet and dry pathogens.

Pursuits of bioweapons research by Canada and the UK were mainly against animals and crops. Offensive research by Germany was forbidden by the government. The USSR effort was relatively small at the time the war ended, and was focused mainly on typhus and plague. Importantly, the available intelligence information collected during World War II was unreliable and often dubious [2].

2.4. Post World War II bioweapons activity and the Biological Weapons Convention

The most notable development in bioweapons control following World War II was the Biological Weapons Convention (BWC) [16] of 10 April 1972, entered into force on 26 March 1975 [2,5–7]. The treaty prohibited development, production and stockpiling of biological and toxin weapons and mandated their destruction. A total of 162 nations signed the BWC treaty. As of January 2001, 144 had ratified it and 18 had signed but failed to ratify. The weakness of the BWC was its failure to provide criteria to separate offensive from defensive BW research and its lack of provisions for on-site inspection and verification. In terms of enforcement, it was and remains toothless.

Compliance, or lack of compliance [2], with the BWC is illustrated in the BW activities of five nations since 1972 (Table 4). There were very large differences between nations with respect to numbers of personnel engaged, in numbers of major facilities, and in weaponizing, stockpiling and use. The UK had no significant program and all activities were discontinued by 1972.

In advance of the BWC treaty, President Nixon of the US, in 1969, ordered discontinuance of bioweapons activity and the destruction of all bioweapon stockpiles. Prior to that time [1,2], 10 of the 11 different BW agents listed in Table 5 had been weaponized, sophisticated delivery systems had been developed, and a huge research program was in place in the US.

By contrast (Table 6), the USSR embarked on a major expansion of bioweapons research about the time the BWC went into effect. BW research was conducted until 1993, and possibly later, in a huge program involving 40–50 institutions with about 60,000 personnel [2,8] (see Table 4). The work was carried out by the Ministries of Defense, Agriculture, and Health, by the Biopreparat Institutes, and by the Academy of Sciences. Violation of the BWC became evident in 1979 with the accidental aerosol escape of anthrax spores from the weapons site at Sverdlovsk [5,8,86,100] with the resultant killing of many people and animals by inhalational anthrax downwind from the plant. The human death toll was not established but likely numbered into the hundreds. Among the agents listed in Table 6, between 10 and 12 weapons were developed [2]. In addition it was noted [2] that the USSR program included pursuit of genetically modified agents.

Iraq (Table 7) was a late entrant into major bioweapons research and development, starting in 1975, the same year that the BWC treaty went into full effect. The long list of agents reported to have been weaponized or only researched [2,8–10] poses a formidable threat, if being continued at the

Table 5
Bioweapons agents in the US bioweapons program 1945–1969

Weaponized	Weapons systems
Bacteria	Sergeant missile warhead
Anthrax[a]	
Tularemia[a]	
Brucellosis (*B. suis*)[a]	Spray dispenser for drones
Q fever[a]	
Virus	Wet and dry spray tanks for jet planes
Venezuelan equine encephalitis[a]	
Yellow fever	
Toxins	Cluster bombs
Botulinum[a]	
Staphylococcal enterotoxin[a]	
Antiplant	Bomblet dispenser for long range bombers
Rice blast	
Wheat stem rust	
Rye stem rust	
Research only—numerous	

Source: [1,2].
[a] Weaponized and stockpiled.

Table 6
Partial list of bioweapons reported to have been researched, developed, some weaponized by 1993 by the USSR

Bacteria
Anthrax
Tularemia
Brucellosis
Plague
Glanders and melioidosis
Virus
Smallpox
Venezuelan equine encephalitis
Japanese encephalitis
Russian spring–summer encephalitis
Viral hemorrhagic fevers
Filovirus—Ebola
Filovirus—Marburg
Filovirus—Lassa fever
Bolivian hemorrhagic fever
Argentinean hemorrhagic fever
Research on genetically modified agents was pursued

Source: [2].

present time. Also threatening are the systems of weapons delivery. Following the invasion of Kuwait and the defeat of Iraq in the Persian Gulf War, much reliance was placed on the inspections that were carried out by the United Nations Special Commission (UNSCOM) under the UN agreements with Iraq which ended the conflict [8]. Inspections are presently deterred. Until full inspections can be reinstated, there is much concern for continuance of covert pursuit of bioweapons [10,11]. An Iraqi defector made allegations of at least 20 hidden weapons sites in Iraq [12].

The South African program [2] (Table 4), pursued from 1981 to 1993 was small in number of workers and of disease targets, mainly anthrax and Clostridia species, including *Clostridium perfringens*. Anthrax and cholera agents may have been studied but without weaponization research.

Table 7
Reported bioweapons pursued by Iraq from 1975 to the end of the Gulf War and beyond (?)

Weaponized	Researched
Bacteria	Viruses
Anthrax	Infectious hemorrhagic conjunctivitis (Enterovirus 70)
C. perfringens	Rotavirus
	Camelpox
Antiplant agents	Possible others (speculation)
Wheat rust	Plague
Toxins	*Salmonella*
Ricin	Smallpox[a]
Aflatoxin	*Brucella*[a]
Botulinus	Trachothecene mycotoxins[a]
Weapon systems for delivery	
Missile warheads	
Aerial bombs	
Dispenser/drone aircraft	
Helicopter spray	

Source: [1,10].
[a] Purportedly declared by Iraq.

It is outside the scope of this review to state or to suggest which nations of the world might be engaged in offensive bioweapons research in the contemporary time period. It is possible that weapons programs may be in far greater number than ordinarily believed, emphasizing the need for aggressive pursuit of means to protect against them. Henderson, in his testimony to the US Congress on 5 September 2001 [13] stated that "intelligence agencies have estimated that at least a dozen states possess or are actively seeking an offensive biological weapons capacity." Others [2,14], collectively listed a larger number of countries based on information derived collectively from five different sources.

2.5. Enhancing the effectiveness of the Biological Weapons Convention

As noted above (Section 2.4), the BWC [2,5,16] made no provision, at its inception in 1972 and in its 5-year meetings in 1980, 1986, 1991, 1996 and 2001, to verify and enforce compliance with the treaty which has been ratified by the 144 national signatories. As before, no agreement on enforcement could be achieved in 2001 (see [7,9,15,16]) primarily because of the position of the US that intrusive inspections of "dual-use facilities" with perceived bioweapons capabilities would be an open invitation to industrial espionage of proprietary information of the pharmaceutical and biotech industries [17–20] and of secrets of the US defense organization as well. Even academia [21] would be under surveillance and compliance requirements. The UK position [22] was less adamant against inspections. Alternative proposals made by the US [23] were not accepted by the other nations and it was agreed at the end of the 2001 session that the meeting would be continued in 2002. In the absence of BWC enforcement, there is increasing need to develop means to address all possible bioterrorist threats [24]. It is equally important to domestic [25] as well as international terrorism.

The matter of achieving the BWC agreement had been very badly prejudiced by the intrusive inspection of the Pfizer pharmaceutical plants in Terre Haute, Indiana and Groton, Connecticut [5,20] under the Trilateral Agreement of 1992 between Russia, the UK, and the US. In 1992, at the time of the admission by the Russian Yeltsin government that BW treaties had been violated, it was agreed that representatives of Russia, UK and US would meet in Moscow to make a trilateral agreement [5] which would strengthen the intents of the BWC among the three nations. The agreement was only for visits but was turned into inspections [5] and that, together with false accusation of continuing US biological weapons research in the Russian report [5,20] has illustrated the damage that a "toothful" BWC might do.

Table 8
Examples of possible genetic modification of viruses and bacteria in bioweapons development

Genetic modification of microorganisms opens the way to "limitless" possibilities in bioweapons development
Examples:
Induction of resistance to antibiotics and drugs through transfection with plasmids or through genetic modification
Genetic alternation of pathogens to:
Expand or change host and host cell tropisms
Convert commensals or weakly virulent organisms to lethal pathogens
Alter antigenic composition to evade immunity
Incorporate gene sequences expressing lethal toxins
Incorporate gene segments encoding inappropriate cytokines

3. Genetic modification of microorganisms

Although genetically modified organisms have not achieved stature among BW microbes, such pursuit was reported to have been made by the USSR prior to 1993 [2] (see Table 6). Successful accomplishment of genetic modification would create almost "limitless" new possibilities [26,27] for weapons development, as listed in Table 8. A recent example was that of altering the virulence of mousepox (ectromelia) [28] by modification of the virus to express the IL-4 cytokine. This rendered it highly lethal for ordinarily resistant strains of mice. As another example, it was recently reported [29] that the genetic sequence of camelpox virus is very closely related to that of smallpox, suggesting that smallpox virus might be created genetically from camelpox virus, posing a smallpox threat.

4. Tools for defense against bioweapons

The biological means for defending against bioweapons (Table 9) include prophylactic vaccines against infectious disease agents, and therapeutic substances consisting of antibiotics, antiviral drugs, and antibodies for passive protection. Biodetection and espionage to discover and eliminate clandestine activities will be aided by instrumentation for rapid forensic detection and analysis of biological agents. Beyond science, there are the tools of diplomacy and negotiation, and engagement by the world community in the imposition of fairness in resolution of international disputes.

Table 9
Technologic tools for defense against bioweapons

Prophylactic vaccines
Therapeutic substances
Antibiotics and antivirals
Monoclonal antibodies
Biodetection and elimination of illicit pursuits
International espionage to discover and identify clandestine activities
Instrumentation for forensic detection and analysis of bioweapons
research, development and deployment

Table 10
Infectious disease agents against which there are licensed vaccines in the US

Viral	Kind[a]	Bacterial	Kind[a]
Measles	L	Diphtheria	K
Mumps	L	Pertussis	K
Rubella	L	Tetanus	K
MMR combined	L	DTP combined	K
Varicella	L	*Meningococcus*, and conjugate	K
Poliomyelitis	L and K	*Pneumococcus*, and conjugate	K
Yellow fever[b]	L	*H. influenzae*, and conjugate	K
Adenovirus	L	**Tuberculosis (BCG)**[b]	L
Smallpox[b]	L	**Cholera**[b]	K
Hepatitis A	K	Typhoid	K and L
Hepatitis B	K	**Anthrax**[b]	K
Influenza	K	**Plague**[b]	K
Rabies	K		
Japanese encephalitis[b]	K		

[a] L: Live; K: Killed.
[b] Bold: US recognized bioterrorism agents. Plague vaccine was recently discontinued.

Though vaccines may have great potential for disease prevention, they are of little or no use as therapeutics. Table 10 lists 13 viral and 10 bacterial diseases for which useful vaccines have been developed and licensed [30] for routine distribution in the US during the past century, not counting smallpox vaccine which was developed in 1796 and used until the smallpox virus was eradicated. Added to this are immune globulins (not licensed) for inducing immediate passive immunity [31,32]. These products certify the successes of vaccines and immune globulins, and provide models for pursuit of additional vaccines and antisera in the future.

In contrast to the number of vaccines, there are numerous potential agents [33,34] capable of use in preparing bioterrorist weapons. The Australian group (see [35]) lists 65 different agents for export control. The present most likely biological weapons to be used in bioterrorist attacks are those of anthrax and smallpox [36]. Fortunately, effective vaccines exist for both agents but present vaccines against them are less than ideal and are presently in short supply.

Present *anthrax vaccine* [36–39] has excessive reactogenicity and requires many doses (six shots over a 2-year period). New regimens to reduce doses are under study by the Centers for Disease Control and Prevention (CDC) [37,40,41]. Means for improvement of the vaccine by removal of residual toxins and impurities are simple and are also under present investigation, together with pursuit of myriad of alternative possibilities which include recombinant expression of protective antigen (see [42]).

Smallpox virus [36,39,43,44] which was eradicated by 1977, became a prime candidate for bioweapons attack after vaccination, worldwide, was discontinued. The fear is that covert supplies of smallpox virus may reside in rogue laboratories outside WHO-approved storage at the State Research Center of Virology and Biotechnology in Koltsovo, Siberia, Russia, and at the CDC in Atlanta. The US national supply of vaccine, which includes dose reduction by dilution [45], will suffice to vaccinate the total US population by the end of 2002. The problem with the current US vaccine is that it is not entirely safe and will kill about two persons in every million vaccinees who receive it [39,44,46]. In addition, numerous persons will have serious side effects. Two plans for vaccine use have been proposed. The one calls for universal voluntary vaccination [47] and the other is based on containment by ring vaccination and quarantine after the disease appears [48]. The pros and cons are sufficiently evident to elicit a proposal that there be a national dialogue for determination [46]. Universal vaccination appears to be the only means to approach vaccine control since smallpox may be introduced simultaneously at a number of different sites in the US [46].

5. Problems with vaccines

There are many problems to consider and large hurdles to cross in the development of new prophylactic vaccines (Table 11). These include need to give vaccine in advance of exposure, multiple dosing, high cost and long term requirement for development of most vaccines. The enormity of different possible antigenic specificities to cover, of need for stability on storage and the requirement to evoke durable immunity, of restrictions as to acceptable reactogenicity, and of immense costs for production and stockpiling vaccines that may never be used. Added to this is the possibility for deliberate manipulation of bioweapons agents to change their antigenic specificity, rendering them non-protective, and the feasibility to turn commensals into pathogens by genetic alterations.

Table 11
Problems with vaccines

Vaccines are prophylactic, and killed vaccines may require multiple doses
The time required for development of a new vaccine may number 8–10 years at a cost approaching US$ 500 million
There is enormity of numbers of types, subtypes and strains of agents with different antigenic specificity
Vaccines must be stable on storage and immunity needs to be durable
There is restriction in allowed reactogenicity
Cost of stockpiling vaccines may be immense and it is unlikely that most will never be used
Antigenic specificity may be deliberately altered by genetic manipulation, and even commensal saprophytes can be rendered pathogenic

Table 12
Selective focus on potential bioweapons according to assessment of threat to civilians (categories established by the CDC)

Category		
A	B	C
Anthrax[a]	Q fever	Nipah virus
Smallpox[a]	Brucellosis	Hantavirus
Botulinum[a]	Glanders	Tick-borne encephalitis
Plague[a]	Ricin toxin	Yellow fever[a]
Tularemia	*C. perfringens* toxin	Multidrug resistant TB[a] (BCG)
Viral hemorrhagic fevers	Staphylococcal enterotoxin B	

Source: [36].
[a] Agents for which there are licensed vaccines or antisera in the US. Plague has been withdrawn from the market.

5.1. Prioritization of vaccine development

Efforts have been made to reduce the enormity of the problem for defense against bioweapons through ranking of disease agents in categories based on assessment of risk. The US CDC recently listed 17 bioweapon disease targets in 3 categories of priority: A, B, and C [36,49], as shown in Table 12. Among these agents, only six vaccines or antisera are presently licensed in the US. The category of the hemorrhagic fevers (Table 13) is a complex of at least 50 highly virulent disease agents which are members of 4 different families of viruses and which generally cause severe and lethal disease [33].

It is important that the National Institutes of Health, particularly the NIAID, which has been charged with the responsibilities for development of plans and for support of an intramural and extramural counter-bioterrorism research program [36]. A research program for category A agents was prepared in February [39]. Categories B and C will follow [36,39,49]. Research emphasis will be on microbial biology, host responses, vaccines, therapeutics, diagnostics and research resources.

Table 13
Complexity of bioterrorism agents causing human viral hemorrhagic fevers

Family	Viral entities
Arenaviridae	Lassa fever South American hemorrhagic fevers (Argentinian, Bolivian, etc.)
Bunyaviridae	Rift valley fever Crimean–Congo hemorrhagic fever Hantavirus (hemorrhagic fever with renal and pulmonary complications)
Filoviridae	Marburg hemorrhagic fever Ebola hemorrhagic fever
Flaviviridae	Yellow fever Tick-borne hemorrhagic fevers (Omsk, Kyasanur forest disease)

Source: [33].

Table 14
Approximate assessment of vaccines for human use against CDC categories A, B, and C agents (definitive information is lacking)

Disease	Status	Comment
Anthrax	**Licensed**	Needs improvement (research)
Smallpox	**Licensed**	Needs improvement (research)
Plague	**Licensed**	Not available, needs improvement
Tularemia	Experimental, IND*	Promise
Viral hemorrhagic fever		
Yellow fever	Licensed	Exemplary performance
Complex of numerous agents belonging to four groups: overwhelming		
Argentinean hemorrhagic fever	In research	Early clinical tests
Rift valley fever	In research	Early clinical tests
Ebola disease	In research	Early research leads
Q fever	Military vaccine IND	Probably satisfactory
Brucellosis	Research needed	Probes in progress
Glanders and melioidosis	Research needed	Probes in progress
Tick-borne encephalitis	**Licensed** for use in Europe and Asia	Needs improved purity
Tuberculosis BCG	**Licensed** worldwide	Needs improved potency
Toxins		
Botulinum antiserum	No vaccine	Polyvalent toxoid in research
Ricin	No vaccine	Probable best approach to protect against toxins is by specific antisera
C. perfringens	No vaccine	
Staphylococcal enterotoxin	No vaccine	

IND: Investigative New Drug regulation, Military. Data from [50] (and other sources).

5.2. Approximate assessment of status of vaccines against priority A, B, and C agents

Table 14 presents an approximate and partially subjective current status summary of the development of vaccines against bioweapons agents, based in large part on Franz et al. [50] plus other reports. Anthrax and smallpox were discussed above (Section 4).

The present US licensed *plague* vaccine is no longer distributed. Improved vaccine is possible [39,51,52] but substantive research will be needed to define the key virulence antigens that can be used in a multivalent vaccine which will be protective against genetically engineered attack organisms. There is no presently licensed *tularemia* vaccine but a live attenuated vaccine has been developed [39,53] which is used to protect laboratory workers under IND regulations. (Table 14). This vaccine is only of limited usefulness but achievement of proof of principle promises improved vaccine in the future. Among the huge complex of *hemorrhagic fever viruses* [54], the licensed yellow fever vaccine is the only example. Vaccines against remaining hemorrhagic fever viruses [39,54–57], are in early research development and special promise is shown for Ebola virus vaccine [57] in which there is priming with recombinant DNA and boosting with recombinant adenoviral vectors. It may be that success with newer approaches, together with the precedents established by the yellow fever vaccine, may light the way to hemorrhagic fever vaccines. *Q fever* vaccine is used routinely by the military for vaccination of laboratory workers under IND regulations [50]. Vaccines, especially live virus vaccines, against brucellosis are pursued mainly for veterinary application. Vaccines against the *Burkholderia* causing glanders and melioidosis, to the author's knowledge, have not been developed and reliance is placed on control by antibiotics. *Tick-borne encephalitis* vaccines are licensed in Europe and the *BCG* vaccines against tuberculosis urgently need to be improved in efficacy. Vaccines against toxins do not exist except for experimental probes with *botulinum* toxoids [39,50,58]. At present, the immune globulins are the only therapeutics for neutralizing toxins. The CDC [59] and the military [50] maintain stocks of polyvalent antitoxins for emergency use and for defense against aerosolized toxin bioweapons [59]. It may be worthy of mention that vaccines against *foot-and-mouth* disease [60] are manufactured routinely to protect livestock against this very serious disease of food animals. Foot-and-mouth disease is presently absent from the US.

6. Assessments for comparative lethality and relative importance of bioweapons agents

6.1. Rank order of killing capability

Thirty years ago, a committee of the World Health Organization (WHO) (Table 15), prepared a rank order for the killing capability of 50 kg of each of 7 agents not including smallpox, delivered upwind from a city of 500,000 population (see [61]). Brucella, Q fever, tularemia and anthrax greatly outranked rift valley fever, tick-borne encephalitis and typhus with respect to numbers of persons incapacitated. The three most lethal agents were anthrax, tularemia,

Table 15
WHO estimates of casualties produced by attacks with biological agents

Agent	Downside (wind) reach (km)	Number of killed	Number of incapacitated
Rift valley fever	1	400	35000
Tickborne encephalitis	1	9500	35000
Typhus	5	19000	85000
Brucellosis	10	500	125000
Q fever	>20	150	125000
Tularemia	>20	30000	125000
Anthrax	>20	95000	125000

Note: 50 kg of agent; 2 km line delivery; downwind; population base 500,000. Source: [61] (original data reported by WHO consultants, Geneva 1970).

and typhus. This exercise provided a working basis to rank the danger from different agents in establishing priorities for vaccine development. It will be noted that the five agents that are last noted in the table are amenable to treatment with antibiotics.

6.2. Infective aerosol dose, prevention, and therapy

In recent time, the US military [50] prepared a list of 10 likely biowarfare agents (Table 16) for which prophylactic immunization or rapid diagnosis and treatment can have an impact on outcome. As shown, there were wide differences in the required infective dose of microorganisms needed to kill. For seven of these agents, there are credible licensed vaccines or vaccines that may be worthy of use under Investigative New Drug (IND) application. For the five bacterial agents, there are antibiotics. For two viral agents, there are antiviral drugs of possible value. Polyvalent immune globulin exists for treating botulinus poisoning. Possibly, specific immune sera will be effective in treating against the hemorrhagic fever viruses.

Table 17
Priority needs for vaccines and therapeutics

Bacterial	Vaccines and antibotics
Viral	Vaccines and antiviral drugs
Toxins	Antitoxins
For all	Stimulants for innate immunity

6.3. Priority needs

The above findings give clear indication of areas in which there needs to be research emphasis and priority (Table 17). Antibiotics [62–65] have long been a mainstay for treating bacterial infections, but have become less reliable because of the development of antibiotic resistance in nature and through their vulnerability to development as bioweapons in which antibiotic resistance has already been genetically introduced. It is fortunate that candidate antibiotics with new modes of action have appeared recently [64,88]. Much can be done to increase the number and kind of bacterial vaccines. Clearly, a major effort to develop new classes and kinds of antibiotics needs to be carried out.

Viral diseases find little present hope for treatment by antiviral substances but it is an area in which the increasing capability to differentiate between host cell and viral metabolisms offers promise for the future [66,67]. It may be of importance that a lipid derivative of an existing drug, Cidofovir [68] may be a lead candidate for treating smallpox, once safety and efficacy for man has been established. As of now, it has been approved by the food and drug administration for experimental treatment for smallpox in the event of a bioterror attack. Many new antiviral vaccines are feasible and are in urgent need of development. In this endeavor, emphasis needs to be placed on polyvalency of preparations and on the development of simplified means for administra-

Table 16
US military list of 10 likely BW agents for which rapid diagnosis and treatment can reduce impact

Agent	Infective aerosol dose	Vaccine	Effective therapy
Bacteria			
Anthrax	8000–50000 spores	Yes	Antibiotic
Brucella	10000 organisms	No	Antibiotic
Plague	100–500 organisms	Yes[a]	Antibiotic
Q fever	1–10 organisms	IND[b]	Antibiotic
Tularemia	10–50 organisms	IND[b]	Antibiotic
Virus			
Smallpox	10–100 organism	Yes	Cidofovir (experimental)
Encephalitis VEE, EEE, WEE	10–100 organisms	IND[b]	None
Hemorrhagic fever complex	1–10 organisms	IND[b]: rift valley fever Argentinean and Bolivian hemorrhagic fever	Ribovirin, immune globulins (for some)
Toxins			
Botulism	0.001 μg/kg	No	Polyvalent immune globulin
Staphylococcal enterotoxin B	30 ng incapacitate, 1.7 μg lethal	None	None

Source: [50].
[a] Removed from market.
[b] Used under Investigative New Drug (IND) Law.

tion as by feeding vaccines derived from recombinant plant tissues [69,70]. Edible vaccines lie well into the future, with the need to standardize antigen content of the vaccine and with control over the kind of response by the immune system which may be induction of oral tolerance as well as protective immunity [71]. Passive therapy by antitoxins is a largely neglected approach to providing immediate therapy in event of exposure. A very wide and important avenue to the future is provided by antisera which are capable of reduced cost through recombinant expression of single chain molecules in animals and especially in plants in which they can be kept in long term storage in transgenic seed grains.

6.4. Neglected opportunity: exploration of the innate immune response to protect against bioweapons

In considering biodefense against bioweapons, the author was struck by the absence of studies to determine the possible role that stimulation of the non-specific innate immune system may play in providing ameliorations or solutions for protecting against bioweapon attack. Development of prophylactic vaccines against bioweapon pathogens is hampered by the narrow spectrum immune response of the adaptive immune system, by the length of time required to develop protective immune responses, and by the limitations imposed through the large numbers of important vaccines that need to be developed. There is an alternative approach provided by harnessing the *long neglected* innate immune system (Table 18).

Innate immunity (see [101,102]) is of far earlier phylogenetic evolution in animal phyla than that of adaptive immunity, and resides in essentially all animal species. In most invertebrates, it is the only immune mechanism. The principal cells in the innate immune response system of man are the natural killer (NK) cells, the macrophages and certain of the dendritic cells. These cells bear “toll like” receptors and other binding sites which have broad-spectrum chemical pattern recognition of microbes (including viruses) and their structural substances such as proteins, lipopolysaccharides, capsular material, DNA (especially CpG nucleotide sequences), double-stranded RNA, and the like. These are often referred to as “danger signals.” The activated NK cells and macrophages secrete a number of antimicrobial substances including cytokines (particularly γ-interferon), chemokines, and miscellaneous antagonistic proteins. Complement activation can also occur and may be a beneficial or an adverse event. One can speculate that stimulators of innate immunity (prophylactic or therapeutic), given shortly following microbial attack, may provide broad-spectrum antimicrobial suppressive effects which could make the difference between death or survival of the host. This notion is not without precedent, as revealed by past widespread use of “immunostimulatory” preparations comprised of mixtures of bacterins, nucleic acids, lipids, etc. in Europe and the US during the first half of the last century. Such preparations that had been licensed for use in the US, were abolished in the mid 1900s by the Division of Biologics Standards Regulatory Agency (now CBER of FDA) for want of definition of their mode of action and of definitive evidence for protective efficacy.

In conclusion, it may be timely, in view of the current threat of attack with microbial weapons, to explore “prophylactic–therapeutic” immunostimulation of innate immunity for the possible value it may bring.

Table 18
Neglected opportunity: exploration of innate immune response for protecting against bioweapons

Exploration of protection against microbial bioweapons has not been carried out
Conventional prophylactic vaccines which stimulate adaptive immunity, are of narrow spectrum, are slow to provide protection, and are restricted in practice by the large diversity of possible microbial weapons
Innate immune response is rapid and is provided mainly by NK cells and macrophages
Toll-like receptors have broad-spectrum recognition of microbes and their components
Stimulated NK cells and macrophages secrete many different cytokines, chemokines, and antagonistic proteins
The promise of innate immunity is for antimicrobial suppression which may assist in providing for host survival following attack
Precedent lies in previous long-term use of immunostimulatory preparations comprising mixed bacterins, nucleic acids, lipids, cell wall components, etc
Such immunostimulants were abolished by the regulatory predecessor of the FDA about the mid 1900s

6.5. Protecting food crops

In defending against biowarfare and bioterrorism targeted against man, it must be remembered that the human population can be decimated by lack of food supply as well as by human pathogens. Bioweapons directed against crops can be highly destructive, as discussed by Rogers et al. [72].

7. Venues for research, development and production of vaccines of military importance

For many years, the military establishment in the US has pursued in-house development of vaccines for which there has been no appropriate venue for conversion from proven feasibility to practical and available products. The four principal pharmaceutical companies in the world which are engaged in vaccine manufacture and marketing, might seem to be logical sources for vaccine development and manufacture. In reality, this is not so (Table 19) since public corporations need to give a satisfactory monetary return to shareholders for high-risk engagements and very large investments. Technical feasibility needs to be established before product development and manufacture can begin. The pharmaceutical industry is market driven and must be focused on sustainable markets of sufficient size with adequate

Table 19
Barriers to participation by the pharmaceutical industry in bioweapons vaccine research, development, manufacture, and distribution

Requirement for adequate return to shareholders for high-risk investment
Need for establishment of technical feasibility before major dedication of resources for development and manufacture can begin
Investment in dedicated facilities may be huge and biocontainment may be a large problem
Products are market driven and incentives to participate are based on:
Size and duration of market markup of cost to selling price
Protection of intellectual property
Clinical proof of safety and efficacy; exposure to legal liability
Underestimation of value of product in the public arena is a deterrent to adequate pricing

mark-up in pricing, protection of intellectual property, and tolerable legal liabilities for products. In the world at large, there is gross underestimation of the value which vaccines provide and a reluctance on the part of the payer to buy protection against infectious agents to which he may never be exposed.

These problems are now well-recognized and alternative options are being studied. One such solution [73] which has a chance for implementation is that of constructing a government-owned plant for research, development and production of vaccines for special military needs, which is operated by a knowledgeable corporation. This government-owned, contractor-operated (GoCo) plan that is presently being explored, might be the most reliable approach to assure manufacture of the special vaccines needed for military medicine.

8. A view to the future

8.1. Warfare and weaponry may be outmoded

The pursuit to defend against bioweapons is little more than an engagement to defeat sophisticated new technologies which occupy a niche alongside those of nuclear and chemical weaponry. Warfare, itself, may be outmoded since it is an exercise in which the benefit to cost ratio is unsatisfactory, employing the resources of high technology to bring about human, economic and environmental devastation. Success in achieving resolution of conflict through diplomacy and treaty cannot be relied on, and it may be that some of the tools for those pursuits may also be antique and outmoded. The present may be a time to search for new solutions by identifying and correcting the root causes (see [74]) for war and terrorism.

8.2. The World Economic Forum

The holding of the World Economic Forum (Table 20) of the world's economic and political leaders in New York, after the 11 September 2001 destruction of the World Trade Center, may have been a propitious choice, since it cleared the air from a humdrum past with questions as to the why of biowarfare, the why of terrorism, and the what to do about it. Three topics worthy of discussion here relate to the root causes for terrorism. These include (a) poverty, health and hunger; (b) the role of belief systems in dividing the world's peoples; and (c) the current inadequacy of employment of existing instruments to create integrated systems needed for rapid forensic microbial detection. The last named will aid identification of bioweapons agents and may also provide non-intrusive inspection procedures that will be acceptable for enforcement of bioweapons treaties.

Table 20
Alternative non-biological solutions to the threat of biowarfare and bioterrorism in the venue of the World Economic Forum

Diplomacy and fairness in negotiations to end the incentives for bioweapons programs
Betterment of the human condition
Reducing poverty—adequate food, shelter and clean water
Prevention of disease and improving health
Resolution of conflicts in religious beliefs
Education
Equitable distribution in land disputes
Biodetection and elimination of biowarfare agents
Discovery of bioweapons programs by rogue nations
Advanced forensic instrumentation systems for bioweapons:
Detection and analysis
Enforceable treaties

8.3. Poverty and health

In his opening speech at the Forum, Secretary Powell [75] focused on the US commitment to do battle against the poverty, hopelessness and despair that he perceived as root causes which help to build terrorists' anger. He said we must show them that there is a better way to go. Other participants labeled the 11 September 2001 attack as a wake-up call to the scourges that have bred frustration and anger toward wealthy nations, and to the need to help weak economies, with emphasis on building middle classes in their populations. Domestic bioterrorism in the US may be based on very diverse motivations which reside within individuals and are largely irrational [25].

8.3.1. World health

The above statements at the Forum resonated clearly with the plans and programs initiated by Dr. Brundtland, Director General of the WHO, who emphasizes the role of global health in achieving global economic development and in ending the poverty gap. In January 2000, Dr. Brundtland [76] formed the "Commission on Macroeconomics and Health" to examine the place of health in global economic development. The Commission report [77] under the chairmanship of Jeffrey Sachs [78] was issued in December 2000. In her comments on the report, Dr. Brundtland pointed out that an

expenditure of US$ 66 billion per year for 10 years could end 8 of the 12 million deaths from infectious diseases per year in the developing nations. The economic return for this investment would be US$ 360 billion per year, half through extending healthy lifespan, and half through direct benefits deriving from increased economic productivity. Much of this would be achieved through application of existing vaccines and by development and use of new vaccines.

Following on the Sachs report, the WHO and sister organizations launched a new initiative at the World summit on 2 February, initiating implementation of a new report titled, "Scaling Up the Response to Infectious Diseases: A Way Out of Poverty." The focus in the report is on AIDS, tuberculosis and malaria.

The WHO initiative will be aided by the Global Fund to fight AIDS, tuberculosis and malaria [79], by the Gates Foundation's [80] initiatives in vaccine development and use, by the Global Alliance for Vaccines and Immunization (GAVI) [81], and by a worldwide solicitation of public and private funding, targeting for US$ 27 billion by 2007. The aggressive pursuits to provide health and to end poverty in the developing nations would bring much value to the developed nations through assuring supplies of raw materials from natural resources and in creating markets for finished goods.

8.4. Hunger

The new millennium finds a world in which nearly one-sixth of its peoples face poverty and hunger. These are conditions which contribute to grievances which can feed bioterrorism. There is confidence [82] that science has the know-how to increase food productivity and to provide solutions to the world of the poor. One activity of the moment is of seminal importance as applies to improving the production of rice [83,84] which is a staple for half the world's peoples. The recent progress [83] by the publicly funded International Rice Genome Sequencing Project (a consortium) and by the privately funded Swiss Syngentia (Torrey Mesa Research Institute) in sequencing the genome of two major subspecies of rice has great portents for increasing productivity and disease resistance in plants essential to the world food supply and its need to expand to accommodate future population growth. When completed and implemented, increased grain productivity will be a major triumph for science in solving world problems.

The value of applying science to rice production may come from reengineering the cultivar at the biochemical level, increasing photosynthetic and other activities and increased productivity. Adding maize genes to rice plants is also contemplated [83]. Achieving increased efficiency in rice production may be daunting but stands high on the world's priorities. A new crossbreed for rice of African and Asian varieties has recently been shown to give marked increase in productivity over the present African variety [85].

8.5. Religions and science

An issue was raised at the World Economic Forum relating to the tension between the world's religions as a basis for conflict. In her recent book, "The Battle for God," [87] Karen Armstrong provides some clues for explaining terrorism carried out for religion and state. She points to a contemporary resurgence in many areas of the world of religious fundamentalism which rejects the economic benefits that science and modernity can provide. Militant piety, she says, may give rise to rage, resentment and revenge which distorts the basic tenets of the religion itself. Rejection of modernity is a root cause for the poverty which accompanies societal and economic dysfunctions. Taking a clue from Karen Armstrong, the time might have come for the world to focus on similarities rather than differences in its belief systems, and to conduct a campaign that will reduce institutionalized prejudices and elevate the human condition giving rise to rewards in may bring. Education is key to success in that endeavor.

8.6. Forensic biodetection systems and enforcement of treaties

The largest deterrent to detecting the development and fielding of biological weapons by rogue nations has been the lack of ability to enforce treaties such as the BWC (see Section 2.4 above). This agreement has no means to verify compliance with the Convention through inspection and detection of covert activities. Equally important is the detection and identification of foreign or domestic terrorists who choose to conduct asymmetric warfare using bioweapons at their disposal. This problem is one for which technologic capabilities do exist [89–92].

Notably lacking in the biodetection initiative has been a failure to assemble existing technology and tools to create working systems for rapid forensic detection, analysis and identification of the existence and the place of origin of human and animal pathogens being applied to bioweapons, development, production and use [93–99]. Toward this end, many existing technologies may be applied with special emphasis on PCR analysis and on immunologic identification employed in biosensor systems. A robotic, rapid throughput laboratory would focus on molecular determination of the phenotypic and genotypic features of a wide range of potential bioweapon agents in overt or covert locations and in outbreaks of disease suspected to lie outside natural occurrences.

A system for biodetection purpose would consist of both portable biodetection and identification equipment, and of a global network of central laboratories with capabilities for confirmation and for precise analysis and identification of biological agents. Importantly, such single, high speed, high volume systems would provide the tools whereby detection, deterrence, prevention and response can be accomplished. A global network of regional laboratories is urgently needed.

Beginning work on this initiative consists of consideration for development and proof of capability of a single model laboratory. Dr. Scott Layne [89–92] physicist, physician, and epidemiologist is an academic leader in this initiative, and is in active pursuit of such an end.

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