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Humans have long suffered the effects of disease causing biological agents. Today
bioterrorism appears to be on the rise while at the same time global and ecological
changes have resulted in the emergence of new diseases. Potential repercussions of an
epidemic pose immense challenges requiring a methodical approach to align priorities
and resources. Past assessments evaluating the potential impact of an introduction of
various biological agents have often produced disparate results, primarily due to
underlying differences in their comparison methodologies and data inputs. Divergent
outcomes of these studies have resulted in very broad biopreparedness strategies without
a consensus on how to target limited resources on just those agents that could have the
greatest public health impact. Further hampering biopreparedness is a paucity of data not
often recognized due to reliance on subject matter experts and qualitative processes. In
consideration of these challenges the present study evaluated thirty three bacterial and
viral agents using the full range of available data in the scientific literature. Quantitative
metrics were combined to rank the potential impact posed by an agent, relative to others
considered. Resultant rankings were obtained for low, most likely and high potential
public health impacts for both untreated and treated mortality endpoints. Through the
incorporation of the full range of available data, results of the current assessment made
strides to unify conflicting outcomes obtained in past assessments.

Public Health Impact Assessment,
A Science-Based Methodology for Comparing Biological Agents

by
Julia R. Appt

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I understand that my thesis will become part of the permanent collection of Oregon State
University libraries. My signature below authorizes release of my thesis to any reader
upon request.

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Julia R. Appt, Author

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TABLE OF CONTENTS

TABLE OF CONTENTS (Continued)

TABLE OF CONTENTS (Continued)

LIST OF FIGURES

LIST OF TABLES

PUBLIC HEALTH IMPACT ASSESSMENT,
A Science-Based Methodology for Comparing Biological Agents

Introduction

Biologic agents (bacteria, viruses, or toxins) have long been intertwined with historical and political events. One of the most infamous examples occurred when the Tartar army, laying siege to the city of Kaffa catapulted the bodies of plague victims into the city. This action broke the siege but led to the second widespread outbreak of plague caused by the migration of fleeing, infected Kaffa citizens. When the plague had run its course almost a third of Europe's population had perished as a result of this intentional biological assault (Bossi et al., 2006). Intentional or man-made use of bacteria, viruses, or toxins for the purpose of inflicting fear, disease and death in a target organism (humans, animals, plants) is today described most commonly as bioterrorism. A culmination of available information, technological improvement and agenda-driven motivation makes the use of biological agents more likely today than at any other time in our past.

A notable example is the anthrax that was dispersed through the United State Postal System shortly after the September 11, 2001 terrorist attacks, resulting in 22 total cases and five deaths (Day, 2003). Deaths from the incident, referred to as "amerithrax", increased fear of biological weapons during an already vulnerable time. In addition to the deaths and psychological trauma, it also became clear that even a small act of bioterrorism could be costly to remediate (Virgo, 2001). Ricin, a toxin derived from a common plant that produces castor beans, has been discovered in London (2003) and Las Vegas (2008) in recent years. Found prior to use in these occurrences, they have none the less illustrated how readily the toxin can be produced. Aum Shinrikyo, a Japan based sect, released sarin, developed as a chemical warfare agent, in the Tokyo subway system, causing 12 deaths and nearly 1,000 hospitalizations (Olson, 1999). The damage inflicted by this sect could have been even worse, as it had long sought biological agents like the Ebola virus and even developed laboratories for the production of *Bacillus anthracis* (anthrax) and Botulinum toxin (Olson, 1999). Fortunately they never succeed in obtaining and cultivating a biological organism for use in their apocalyptic vision.

Indeed mal-intent is not needed to cause interruptions in normal social and economic patterns. At the same time that human motivation for the use of biological agents appears to be on the rise, global and ecological changes have resulted in the emergence of new

diseases. Deforestation and expanding urbanization, coupled with changing global climate patterns, may play a role in a new round of emerging infectious diseases such as those caused by *Paramyxoviridae* Hendra and Nipah viruses or the evolving influenza virus that has manifested most recently as H1N1 (swine flu) and H5N1 (bird flu). The recent H1N1 influenza outbreak (2009) has caused many deaths, closed public gatherings, and restricted travel as it circles from one hemisphere to another (Katz, 2009). Prior to the emergence of the H1N1 strain, similar concern for the H5N1 (avian flu) strain was noted and has been closely tracked since 1997.

The intentional use of biological agents occurs sporadically. Natural outbreaks, on the other hand, continue to occur at a sustained pace despite medical research and technological advances. Naturally occurring outbreaks develop when conditions place humans or intermediate vectors (organisms that transfer disease from one host to another) within the normal habitat of a biological agent. These conditions are most often random, only identifiable with the benefit of hindsight. Intentionally spread diseases on the other hand have predictable barriers (production, storage, dissemination) that must be overcome in order to initiate an outbreak in humans. A distinction can begin to be made about those biological organism that pose the greatest public health impact to humans by examining and identifying how each biological agent would relatively succeed or fail to overcome these barriers.

Biological outbreaks, be they intentional or natural, that occur in isolated areas are magnified through international travel and insufficient epidemiological surveillance practices. Technological advances that have improved the ease of information sharing through multiple media pathways make it possible for previously complex biological processes and laboratory techniques to be demonstrated and disseminated to an unlimited audience (Anderson, 2003). Globalization also increases the probability that health impacts and monetary losses will not be confined to one initial hot spot.

Taken together, bioterrorism and emerging biological agents are applying increasing pressure to public health planners and government officials around the world; pressure that provides motivation to drive scientific research and strategic policy discussions. Failing to adequately assess the nature of the problem would result in biosecurity vulnerabilities. Biosecurity refers to the actions taken to avert disease and secondary

effects that result from the spread of a biological agent. Biosecurity is one component of biopreparedness, a comprehensive effort to prevent both intentional and natural outbreaks as well as limit the consequences should an outbreak occur. The other component of biopreparedness is biodefense which describes defensive actions taken to protect against outbreaks.

In order to prioritize the use of limited financial resources, assessments and evaluations have been conducted on select biological agents to determine their public health impact. Two styles of bioassessments have typically been performed. The first and most common evaluation method ranks the potential impact, or threat, posed by an agent, expressed as a combination of key characteristics to differentiate high consequence agents from lower consequence agents. The second style of bioassessment involves the use of probabilities to determine the agents that present the greatest hazard to the public. In this instance, risk would be the probability that a particular agent would create a public health event multiplied by the projected impact or effect. Risk, defined as likelihood multiplied by consequence is difficult to derive, especially for bioassessments where inputs are constantly changing. Determining appropriate probabilities of rare events, often without the assistance of historical statistics, is an arduous task involving a great amount of uncertainty. Given the difficulty of evaluating risk, most assessments that have been performed to date describe endpoint consequences without assigning a traditional risk metric. A pre-determined scenario can be incorporated into either type of assessment. Scenarios have been used to provide boundaries and conditions that subject matter experts take into consideration before providing input.

The desired result of either assessment style is to obtain a rank ordered list that provides a comparison among the potential consequences of the considered agents. Policy makers use these reports to inform decisions on the amount and priority of support needed to minimize the dangers posed by specific biological agents or groups of agents. Several assessments comparing the potential impact(s) of biological agents have been performed to aid decision makers. However, a lack of available data, limited transparency, and a heavy reliance on highly subjective subject matter expert opinions, compounded by scenario-based assumptions and non-uniform qualitative analysis, has hampered efforts to provide decision-makers with a clearly communicated and easily

defensible approach to address the problem.   Inconsistent results due to fundamentally different frameworks offer little assistance to policy makers who must piece together information to discern a complete biopreparedness strategy under significant resource constraints.

To address these concerns, this study developed a science-based methodology to allow rapid assessment and comparison of potential public health impacts resulting from any biological agent. Public health impact refers to the potential for an agent to burden society based on characteristics related to its availability, growth, stability, ability to spread, lethality as well as available countermeasures and controls. The focus of the methodology is to establish an easily communicated and defensible scientific approach that utilizes only referenced, quantifiable data. Specifically excluded from the methodology are scenario-based models, as approaches of this nature require untested inputs developed by hypothetical adversaries and are highly reliant on the subjective expert opinion.

Literature Review

Government agencies, mandated by the Homeland Security Presidential Directive 10 (HSPD-10), are the primary sponsors of biopreparedness assessments. In the United States several agencies pursue analysis informing the separate, but overlapping, realms of public health, homeland security and food safety. Arguably the most invested agencies are the newly formed Department of Homeland Security (DHS), Department of Defense (DoD), the Food and Drug Administration (FDA) and the United States Centers for Disease Control and Prevention (CDC). The Food and Drug Administration has been slow to respond to bioterrorism concerns; however, the recent appointment of Dr. Margaret Hamburg, a biodefense expert, as Commissioner of the FDA highlights the growing attention paid to the safety of the global food supply. The Department of Defense has primarily been concerned with research of biological agents for both offensive and defensive purposes. With the possible exception of the DoD, the CDC leads other agencies with regard to the study of potential impacts resulting from biological agents, and is responsible for the public health considerations associated with biopreparedness planning. Borne out of the September 11, 2001 terrorism attacks, the DHS has inherited the responsibility for bioterrorism planning and response in the United States per HSPD-10.

As demonstrated by the emergence of the H1N1 influenza virus, global outbreaks require the marshalling of international resources. The leading agency on the global stage is the World Health Organization (WHO). Famous for the strategic eradication of smallpox, WHO is a key multinational agency consisting of 193 member states advocating for the cooperative prevention of, and response to, biologic outbreaks, by promoting health security (World Health Organization, 2009). Composed of government representatives of states-parties to the Biological Weapons Convention (BWC) signed in 1975, the Ad Hoc Group has a mandate to establish legally binding strategies for the enforcement of the BWC (United States Department of State, 2009). Another multinational agency, the European Union (EU) also contributes research and ongoing dialogue to the field of biopreparedness as it attempts to unify the collective efforts of many countries to improve outbreak surveillance in its region. The European Union is also a member of the Australia Group. The Australia Group is comprised of 41 member

states who informally work together to meet the objectives of the BWC through export controls to limit development of biological weapons (Australia Group, 2009).

The status of the field can be derived from a review of recent assessments sponsored by principal agencies, including those domestic and international agencies described above. The next section provides an overview of the leading assessments currently informing the field of biodefense and biosecurity. Following a discussion of each methodology and its associated results, a summary of the strengths and weaknesses of each approach is provided. This synthesis of information provides the foundation for the research approach used in the present study.

Department of Homeland Security

To meet the intent of the Homeland Security Presidential Directive 10, the Department of Homeland Security released its first assessment, the Biological Agent Risk Analysis (BARA) in 2006. The goal of the BARA analysis was to provide a logical framework to identify and assess the risk of high consequence biological agents. The report and its outcomes are classified; however, we can gain insight into the report's methodologies by examining a critique published by a committee of the National Academy of Scientists (NAS) in 2007. The Committee on Methodological Improvements to the Department of Homeland Security's Biological Risk Analysis, jointly sponsored by DHS and NAS, was composed of thirteen members from diverse academic disciplines. The goal of the Committee was to identify strengths and weaknesses in the DHS assessment. It should be noted that neither the Biological Agent Risk Analysis nor its outcomes were available for review by the NAS committee. As a result, the critique was based on interviews with officials from DHS and supporting agency partners involved in developing the risk analysis.

From the critique we gain the knowledge that DHS conducted a probability risk assessment of 28 biological agents believed capable of causing harm to the public as a result of an intentional release. Probabilistic risk assessments are commonly used in nuclear and chemical safety fields to manage risk from known hazards (United States Nuclear Regulatory Commission, 2007). The assessment followed a 17 step model along different event pathways as a simulated bioterrorism attack unfolded from the planning stages, through public exposure, to end-point consequence. Each event tree pathway

represented a unique scenario with an individually associated probability of occurrence. Scenarios differed based on the attack characteristics, such as pathway of exposure or environment of release (outdoors, indoors).

Major endpoints of interest for DHS were mortality, morbidity and direct economic impacts. Endpoints of interest are the consequences of combined characteristics such as infectivity, incubation, and transmissibility, which are specific to a certain agent. Agent characteristics can be derived from available information when possible; however, there is a paucity of available information especially on biologic agents rarely expressed in the human population and therefore poorly understood. As a result, subject matter experts (SMEs) are often heavily relied upon for the extrapolation of data gaps. SMEs are individuals prominent in the area of study being examined. Their knowledge and opinions are often relied upon when incomplete data hampers quantitative assessments. As with other assessments, SMEs provide the core input for DHS's report (NAS, 2007). Yet there is some question whether SMEs provide equal representation of the biologic agents (Krause, 2008). In some assessments, the composition of subject matter expert panels is not even disclosed, as was the case in the DHS report. Ultimately, reliance on SMEs input lessens the report's overall credibility due to a lack of transparency coupled with a high degree of uncertainty. In other words the outcome was a produced by unknown inputs. The Committee summarized their critiques of the 2006 DHS report in the following manner:

1. Probability risk assessments with event tree pathways remain ill equipped to describe a thinking adversary capable of adjusting to biodefenses or conducting multiple attacks at once.
2. As much as subject matter experts offer, each one brings with them biases and individual knowledge gaps.
3. The method of probabilistic risk assessment does not allow DHS to measure how shifts in resource allocation will impact public health consequences. Rather than emphasize a risk management approach it focuses on the probability of use.
4. The assessment fails to include a measure of confidence in the data.

Centers for Disease Control and Prevention

In a summary report for the CDC publication *Emerging Infectious Diseases*, Rotz et al. (2002), presented a methodology which categorized biological agents, in an effort to

standardize bioterrorism research priorities. A panel formed by subject matter experts from the Department of Health and Human Services (HHS) worked together with various intelligence services and law enforcement organizations to develop the process outlined by Rotz et al (2002). Criteria of interest, metrics and a rating scheme were selected by the panel after a review of classified as well as unclassified literature (2002). The CDC summary used a qualitative ranking scale (0, -, +, ++, +++) to indicate the spectrum of impact of a particular biologic agent attributed to the criteria described at the top of Table 1. To further describe each criterion, additional sub-categories were identified as:

1. Agent availability
2. Prescribed biosafety level
3. Exposure pathways
4. Environmental stability
5. Number of times the agent has appeared in media reports over the course of a year
6. Required stockpile of anti-microbial/anti-viral treatment therapies
7. Surveillance systems
8. Current diagnostic capabilities

Each agent was then evaluated and scored by the SMEs, using a sliding scale that ranged from no impact (0) to a large impact (+++).   In the end, one point was added to an agent's overall score for each "+" mark received.   The number of total points for an agent was then compared to pre-selected cut-off values for final placement into one of three categories, denoted as A, B, and C. Biologic agents placed into category A are those viewed as potentially causing the highest degree of harm to the health of the general public. These agents were also believed to have the ability to be disseminated to the largest number of individuals. Category B agents represent moderate health impacts less suited for broadcast dissemination and also tended to be more obscure than category A agents. Lastly, category C agents signify emerging diseases that should be watched and studied in the event they evolve into agents with the potential for higher levels of harm. The results of the analysis grouped 16 biologic agents or groups of agents into either category A or B. Additional agents were selected for category C, but were not specifically listed in the report. Based on their potential impact, Rotz et al., (2002) concluded that category A agents should have priority over other agents when allocating resources to improve preparedness.

Table 1. Centers for Disease Control Assessment Results

Rotz et al. (2002) developed this table in their sentinel article, one of the first to rank biological agents by potential impact. While not detailed in this figure, category C agents are described as emerging threats.

Disease	Public health impact		Dissemination potential		Public perception	Special preparation	Category
	Disease	Death	P-D[b]	P - P[c]			
Smallpox	+	++	+	+++	+++	+++	A
Anthrax	++	+++	+++	0	+++	+++	A
Plague[d]	++	+++	++	++	++	+++	A
Botulism	++	+++	++	0	++	+++	A
Tularemia	++	++	++	0	+	+++	A
VHF[e]	++	+++	+	+	+++	++	A
VE[f]	++	+	+	0	++	++	B
Q Fever	+	+	++	0	+	++	B
Brucellosis	+	+	++	0	+	++	B
Glanders	++	+++	++	0	0	++	B
Melioidosis	+	+	++	0	0	++	B
Psittacosis	+	+	++	0	0	+	B
Ricin toxin	++	++	++	0	0	++	B
Typhus	+	+	++	0	0	+	B
Cholera[g]	+	+	++	+/-	+++	+	B
Shigellosis[g]	+	+	++	+	+	+	B

[a]Agents were ranked from highest threat (+++) to lowest (0).
[b]Potential for production and dissemination in quantities that would affect a large population, based on availability, BSL requirements, most effective route of infection, and environmental stability.
[c]Person-to-person transmissibility.
[d]Pneumonic plague.
[e]Viral hemorrhagic fevers due to Filoviruses (*Ebola, Marburg*) or Arenaviruses (e.g., *Lassa, Machupo*).
[f]Viral encephalitis.
[g]Examples of food- and waterborne diseases.

European Commission

Members of the European Commission's Public Health Directorate developed a threat matrix, comprised of multiple variables, as a decision-making tool (Tegnell et al., 2006). The Commission's objective was to assess different biological agents with the potential

to be used in bioterrorism incidents. The European Commission formed a bioterrorism
task force of subject matter experts to provide inputs for the Commission's threat matrix.
The matrix was first informed by the task force members themselves. Reference material
was used to elucidate remaining data gaps. Additional subject matter experts were
questioned when the literature review was unsuccessful in providing complete
information. Data for each of the variables in the formula were collected and weighted
by consensus of the task force to determine a numerical value for T (threat) out of 20,000
points. Despite the effort to seek out available data and opinions, missing data remained.
Task force members took a conservative approach treating agents with missing data as
higher threat agents compared to agents for which data was readily available.

The Commission's task force combined information into the following formula to
describe overall threat.

$$T = (B * M * A * D) - Tr + C$$

In the formula, T symbolized the overall threat score. As shown here the threat score is
composed of a baseline score (B) that was itself a function of disease burden, death,
person-to-person dissemination potential, and public perception. Death was again
included in the formula as mortality (M), a multiplier of the baseline score. Aerosol
spread (A) and dissemination potential (D) were the remaining multipliers of the baseline
score. Dissemination potential measured both the population's susceptibility to disease
as well as person-to-person transmissibility; the second appearance of this variable in the
formula. Treatment options (Tr) included pre-exposure treatments such as vaccines or
post-exposure treatments, which possibly include vaccines, antiviral or antimicrobial
medications. While treatment reduced the threat score, creation potential (C) increased
the score. Creation potential measured the ease of acquiring or producing sufficient
quantities of an agent, as well as its stability in storage or during dissemination.

Table 2. European Commission's Threat Matrix Results

The two highest threat categories developed by the European Commission was comprised of 35 agents. Agents are listed alphabetically within each category by disease, not by rank.

List of diseases	Agents with very high threat
Anthrax	*Bacillus anthracis*
Botulism	*Clostridium botulinum toxin*
Glanders	*Burkholderia mallei*
Haemorrhagic fever	Congo-Crimean haemorrhagic fever virus, Ebola virus, Guanarito Junin virus, Lassa fever virus, Machupo virus, Marburg virus, Omsk, Haemorrhagic fever virus, Sabia
Plague	*Yersinia pestis*
Smallpox	Variola major
Toxic syndromes	Ricin, tetrodotoxin
Tularaemia	*Francisella tularensis*

List of diseases	Agents with high threat
Brucellosis	*Brucella abortus, Brucella melitensis, Brucella* spp., *Brucella suis*
Cholera	*Vibrio cholerae*
Coccidoidomycosis	*Coccidioides immitis*
Diphtheria	*Corynebacterium diphtheriae*
Dysentery	*Shigella dysenteriae*
Fever	Chikungunya virus
Hantavirus pulmonary syndrome	Hantaan virus
Heamorrhagic fever	Nipah, Rift Valley fever virus
Histoplasmosis	*Histoplasma capsulatum*
Haemolytic uremic syndrome	*Escherichia coli 0157:H7*
Influenza	Influenza virus (new strain)
Legionellosis	*Legionella pneumophila*
Melioidosis	*Burkholderia pseudomallei*
Meningitis	*Neisseria meningitidis*
Monkey pox fever	monkey pox
Neurological syndrome	palytoxin
Paratyphoid fever	*Salmonella paratyphi*
Psittacosis	*Chlamydia psittaci*
Q fever	*Coxiella burnetii*
Rocky mountain spotted fever	*Rickettsia rickettsii*
Scrub typhus	*Orienta tsutsugamushi*
Toxic syndrome	conotoxin, microcystin (cyanginosin), saxitoxin
Tuberculosis	*Mycobacterium tuberculosis*
Typhoid fever	*Salmonella typhi*
Typhus fever (Epidemic louseborne typhus)	*Rickettsia prowazekii*
Viral encephalitis	Eastern equine encephalitis virus, Getah virus, Hendra, (formely: Equine Morbilli virus), Herpesvirus simiae (B virus), Japanese encephalitis virus, Kyasanur Forest virus, LaCrosse, Louping III virus, Lymphocytic choriomeningitis virus, Murray Valley encephalitis virus, Powassan virus, Rocio virus, St. Louis encephalitis virus, tick-borne encephalitis virus, Toscana, Venezuelan equine encephalitis virus, West Nile, western equine encephalitis virus
Yellow fever	yellow fever virus

To assess data confidence, Commission members calibrated the formula utilizing generally agreed upon high and low consequence biological agents. Undisclosed weights were selected by general consensus as described by Tegnell et al. (2006) and applied to the threat formula developed by the Commission. Calibration was validated when outcome results were aligned with expert opinion and scientific literature. Once verified, the Commission used the formula to process data from the rest of agents to derive a threat score for each. Unspecified threshold values were developed to separate biological agents into five different threat levels. Agents reaching the two highest threat levels are displayed in Table 2. Despite arriving at quantitative values for each agent, once grouped into one of the five categories, the relative intra-group rankings were dropped as a way to address inherent uncertainty in the data.

Congressional Research Service

The Congressional Research Service (CRS) provides public policy research and analysis to Congress. In 2004, Dana Shea and Frank Gottron, CRS analysts, published a report for Congress describing the potential outcome of a small-scale chemical or biological attack. From the beginning of their analysis Shea and Gottron (2004) take a different approach than most government assessments. Rather than focus on a large-scale, mass casualty event the report focuses on small-scale attacks. The CRS analysts argued that, if optimally employed, these attacks have the potential to cause significant fear, disease and casualties which would meet with intent of the attack without the need for maximal technical and financial investment. Shea and Gottron addressed their departure from previous assessments by challenging the current biopreparedness assumption that preparing for mass casualty events would also serve as effective preparation for small scale events (2004). In short, different agents may pose greater potential threat for small-scale attacks then those agents ranked higher in scenarios heavily weighted by mass casualty outcomes. Small-scale attacks of this nature may go undetected or poorly managed if biopreparedness strategy remains focused solely on an outbreak from high profile biological agents. The objective of the report was to establish policy implications on a broader horizon of threat awareness then previously reported in other leading bioassessments.

In their biological agent analysis, Shea and Gottron evaluated 30 agents with the potential for use in a bioterrorism attack. Individual agents were evaluated based on the following criteria:

1. Ease of acquisition
2. Ease of dissemination
3. Public health impact
4. Prophylaxis
5. Resistance to available medical treatment
6. Prior weaponization

Shea and Gottron, (2004) forego using an event pathway describing of specific choices a terrorist group may be faced with. Similar to the CDC report, Shea and Gottron's ranking scale is similar to the qualitative scale used by Rotz et al. (2002), with each criteria assigned to one of three categories: low impact (-), neutral impact (0) and high impact (+). Each criterion was equally weighted for the final analysis. Agents were ranked relative to each other based on perceived barriers of use which included acquisition, dissemination difficulty, transmissibility and available medical treatments. Those agents with the greatest number of perceived barriers of use were placed at the bottom of the list while those with the fewest barriers were found at the top of ranking scheme. All criteria being equal, knowledge that an agent had previously been weaponized resulted in that agent being prioritized over other agents with the same score.

The result of the Congressional Research Service report found that agents considered of little concern in mass casualty events rise in consequence potential when evaluated from a small-scale attack perspective, as traditional assumptions about technological sophistication, resources and motivations are relaxed. Given the recent incidences with sarin, ricin and anthrax in which the exposed population was relatively small, Shea and Gottron's perspective is a legitimate one. However, despite the report's increased transparency, its impact is minimized by its qualitative focus.

Biological agents at the top of the list of concern for CRS were glanders, Crimean-Congo hemorrhagic fever, pneumonic plague and hanta virus. In support of their objective Shea and Gottron's study addresses policy considerations surrounding biopreparedness. The results supported their hypothesis that a focus on small-scale

attacks would identify different agents of concern than those focused on in mass casualty consequence assessments.

Table 3. Outcome of the Congressional Research Service Assessment
Agents are listed in descending order of their ranking.

Disease (Biological Agent)	Ease of Acquisition	Public Health Impact	Prophylaxis	Resistance to Medical Treatment	Ease of Dissemination	Weaponized
Glanders (*Burkholderia mallei*)	+	+	+	O	+	Weapon
Crimean-Congo hemorrhagic fever	+	+	+	O	+	Unknown
Pneumonic Plague (*Yersinia pestis*)	+	+	O	O	+	Weapon
Hantavirus	+	+	+	O	O	Research
Dengue hemorrhagic fever	O	+	O	+	O	Research
Eastern equine encephalitis	O	+	O	+	O	Research
Lassa fever	O	O	+	O	+	Research
Russian spring-summer encephalitis	O	O	O	+	+	Research
Western equine encephalitis	O	O	O	+	O	Research
Rift Valley fever	O	O	O	O	O	Research
Marburg hemorrhagic fever	—	+	+	+	+	Weapon
Ebola hemorrhagic fever	—	+	+	+	+	Research
Melioidosis (*Burkholderia pseudomallei*)	+	+	+	—	+	Research
Yellow fever	+	+	—	+	+	Research
Anthrax (*Bacillus anthracis*)	+	+	—	O	+	Weapon
Q fever (*Coxiella burnetti*)	+	+	O	—	+	Weapon
Machupo hemorrhagic fever	—	+	+	O	+	Research
Tularemia (*Francisella tularensis*)	O	+	O	—	+	Weapon
Junin hemorrhagic fever	—	+	O	O	+	Research
Venezuelan equine encephalitis	O	—	O	+	O	Weapon
Typhus (*Rickettsia prowazekii*)	+	O	O	—	O	Research
Rocky Mountain spotted fever (*Rickettsia rickettsiae*)	O	+	O	—	O	Unknown
Escherichia coli O157:H7	+	—	+	+	—	Unknown
Smallpox (*Variola major*)	—	+	—	O	+	Weapon
Monkeyponk	—	+	—	O	+	Unknown
Brucellosis (*Brucella abortus, B. melitensis, B. suis*)	+	—	O	—	+	Research
Shigella dysenteriae	O	+	+	—	—	Unknown
Cholera (*Vibrio cholerae*)	+	—	—	—	+	Unknown
Salmonella Typhimurium	+	—	+	—	—	Unknown
Typhoid fever (*Salmonella* Typhi)	+	O	—	—	—	Unknown

Source: This table was prepared from compiled open source data. Congressional Research Service, 2002 (Updated 2004). See **Appendix C** for detailed data used to generate rating
Note: See text for explanation of symbols. Breaks within the table group agents with roughly comparable rank.

Ad Hoc Group

The Ad Hoc Group of the Biological Weapons Convention continues work to reduce the threat of biological weapons since the convention signing in 1975 (Bossi et al., 2006). The group's Working Paper 356 lists 31 agents viewed by the Ad Hoc Group as having the potential to be used as biological weapons, based on a number of key criteria outlined at the top of Tables 4 and 5.

Table 4. Ad Hoc Group Assessment Ranking, Virus Results

This figure outlines the results of the Ad Hoc group methodology. Here Crimean-Congo hemorrhagic fever, Lassa fever and *Variola major* virus achieve the highest ranking.

Viruses	Weapo-nized	High level of dissemi-nation	Low infection dose	High level of morbidity	High contagiousness (transmissibility man-to-man)	Infection by variety of route (respiratory route)	High level of incapacity/ mortality	Stability in the environ-ment	Difficulty of detection/ identifi-cation	No effective prophylaxis and/or therapy	Ease of produc-tion	Totals +/-
Crimean-Congo HF virus	+	+	+	+	+	+	+	+	+	-	+	10/1
EEE virus	+	+	+	+	-	+	+	-	+	+	+	9/2
Ebola virus	+	+	+	+	+	-	+	-	+	+	+	9/2
[Sin Nombre virus]	-	+	+	-	-	+	+	-	+	+	-	6/5
[Hantaan virus]	+	+	+	+	-	+	-	+	+	+	+	9/2
Junin virus	-	+	+	+	-	+	+	-	+	+	-	7.4
Lassa fever virus	+	+	+	+	-	+	+	+	+	+	+	10/1
Machupo virus	-	+	+	+	+	+	+	-	+	+	+	9/2
Marburg virus	+	+	+	+	+	-	+	-	+	+	+	9/2
Rift Valley fever virus	+	+	+	+	-	+	-	+	+	-	+	8/3
Tick-borne enceph. virus	+	+	+	+	-	+	+	-	+	-	+	8/3
Variola major virus	+	+	+	+	+	+	+	+	+	-	+	10/1
VEE virus	+	+	+	+	-	+	+	-	+	-	+	8/1
WEE virus	+	+	+	+	-	+	+	-	+	-	+	8/3
Yellow fever virus	+	+	+	+	-	+	+	-	+	-	+	8/3
Monkeypox virus	-	+	+	+	+	+	+	+	+	-	+	9/2
Chikun-Gunya fever v. (CHIK)	-	+	+	-	-	+	-	-	+	+	+	6/5
Dengua fever virus	+	+	+	+	-	+	-	-	+	+	+	8/3
Omsk HF virus	-	+	+	+	-	+	-	-	+	+	+	7/4

In their analysis, the Ad Hoc Group evaluated virus and bacterial agents separately to highlight intra-group rankings. At the same time the applied ranking scheme allows for direct inter-group comparison between bacteria and viruses. Through comparison it becomes apparent that bacterial agents generally achieve lower rankings compared to viruses.

Table 5. Ad Hoc Group Assessment Ranking, Bacteria Results

Anthrax (*Bacillus anthracis*), glanders (*Burkholderia mallei*), melioidosis (*Burkholderia pseudomallei*) and plague (*Yersinia pestis*) achieve the highest rank among bacterial agents evaluated.

Bacteria Rickettsiae Protozoa Fungi	Weapo-nized	High level of dissemi-nation	Low infection dose	High level of morbid-ity	High contagiousness (transmissibility man-to-man)	Infection by a variety of routes (respiratory route)	High level of incapacity/ mortality	Stability in the environ-ment	Difficulty of detection/ identifi-cation	No effective prophylaxis (vaccination)	No effective prophylaxis (antimicrobial)	Ease of produc-tion	Totals +/-
BACTERIA													
Bacillus anthracis	+	+	+	+	-	+	+	+	+	-	+	+	10/2
Brucella abortus	+	+	+	+	-	+	-	+	+	-	+	+	9/3
Brucella melitensis	+	+	+	+	-	+	-	+	+	-	+	+	9/3
Brucella suis	+	+	+	+	-	+	-	+	+	-	+	+	9/3
Burkholderia (Pseudomonas) mallei	+	+	+	+	-	+	+	+	+	+	-	+	10/2
Burkholderia (Pseudomonas) pseudomallei	+	+	+	+	-	+	+	+	+	+	-	+	10/2
Chlamydia psittaci	+	+	+	+	-	+	-	+	+	+	-	+	9/3
Francisella tularensis	+	+	+	+	-	+	+	+	+	-	-	+	9/3
Yersinia pestis	+	+	+	+	+	+	+	-	+	-	+	+	10/2

General Contributions

The assessments outlined above provide the most thorough examination of the potential consequences of biological agent release to date. Full assessments that result in an ordered list of agents from low impact to high impact are not the only desirable endpoint for consideration. Discussed below are leading organizations with a stake in biopreparedness and who have contributed to the ongoing preparedness discussion.

The WHO's "Public health response to biological and chemical weapons: WHO guidance (2004)," implies a prioritization scheme by providing detailed information on just 11 of 41 agents listed as potential biological agents of concern. Ordering biological agents in terms of potential public health impact was not the goal of the report; however criteria selected by WHO could inform future assessment reports. For the 11 agents described by the World Health Organization, the information details the relevant facts of disease occurrence, natural reservoirs, modes of transmission, incubation period, mortality, disease manifestations, laboratory diagnosis, required prophylaxis, public health protective measures and medical management.

The United States Army Medical Research Institute of Infectious Diseases (USAMRIID) publishes the *Medical Management of Biological Casualties Handbook.* Like the World Health Organization, the handbook presents detailed information on only a select few agents believed to pose the greatest potential harm. Although military concerns differ from those of the general population, the Department of Defense has conducted research on both offensive and defense use of biological weapons, creating a repository of specialized knowledge within the field, most of which remains classified (Rotz et al., 2002). However, previous military assessments on the impact of biological weapons may not be applicable to non-conventional warfare strategies used by terrorists or as observed in a naturally occurring outbreak. Currently, the DoD is undergoing a revision of its biological weapons threat research to include increased medical awareness. In a recent memorandum to the Surgeon General, Department of the Army, the Armed Forces Epidemiological Board lobbied for inclusion of a medical, risk based analysis rather than reliance on intelligence estimates of adversarial capabilities as has been traditionally done (2001).

Summary Status of the Field

The biopreparedness field has undergone significant growth over the past couple of decades. Previous reports have recognized the importance of assessing select biological agents as a prioritization and decision making tool. The research described up to this point has several commonalities, including strengths and weaknesses that should be built upon or refined, respectively. One weakness is the use of scenario-based assessments. Scenarios apply conditions and restrictions that may not be based in reality. The conditions applied by scenarios, such as mass casualty events or small-scale attacks, have a definitive impact on the outcome (Shea and Gottron, 2004). One overarching restriction has been the focus on man-made attacks despite the prevalence of natural outbreaks. This sole focus on bioterrorism sets limits to the overall significance of each study. None of the reports venture to speculate how each methodology could be used to educate policy makers about the threat posed by each agent under naturally occurring scenarios.

Scenario-based approaches are often informed by intelligence estimates and subject matter experts to determine the probability of occurrence. The Department of Defense was not the only agency to utilize intelligence estimates to determine a probable level of threat posed by a particular agent in the absence of unknown data. Both the Department of Homeland Security and the Centers for Disease Control and Prevention have included intelligence estimates and officials in their assessment methodologies without specification of their reliability (NAS, 2007 and Rotz et al., 2002). Information gained through these sources may be provided without supporting, supplemental evidence. With the benefit of hindsight, history has demonstrated that intelligence estimates as often wrong or poorly understood in their context (Surowiecki, 2005).

Reliance on subject matter expert elicitation was another common thread found in most of the efforts reviewed above. As previously noted, subject matter expert knowledge is considerable, easily assessable and should not be ignored; neither should it be taken on face value. Subject matter expert opinion is varied (Shea and Gottron, 2004). As with any disciple there is ongoing debate about the relative importance of certain criteria which are combined to obtain overall impact. SME opinion does not necessarily represent mainstream views of the field and should be scrutinized for bias affecting data inputs (Krause et al., 2008). When a panel of experts convenes to contribute to an assessment, precautions should be taken to ensure a balance of knowledge is represented. To strengthen the level of transparency and confidence in the results, a published list of panel members should be presented along with findings.

With the exception of the European Union's threat matrix, previous studies have relied on qualitative methods to perform their assessments. As reviewed, qualitative processes were subjective in nature. Cut off points and weights (the difference between a "-" and a " +" or a "+" and "++") were not disclosed. As with the DHS probalistic risk assessment, Rotz et al. (2002) provided no measure of confidence in their underlying metric ratings. Under these circumstances, a lack of transparency and reliability on both inputs and analysis fundamentally limit the reliability of these studies (Krause, 2008). Despite the European Commission's quantitative advancement, there remained a lack of transparency in the data used in their model, as SME's were chiefly responsible for

providing inputs. Shea and Gottron's effort improved upon transparency standards in the field when they provided reference appendix tables describing their qualitative findings.

Measures of uncertainty were largely lacking in the reviewed assessments, however the recent effort by the European Commission addressed uncertainty in two ways. The first method was through a specified means of calibration not previously addressed. A concerted calibration method reduced uncertainty in the process while outcome uncertainty was addressed by dropping the intra-group rankings of the five delineated threat groups.

Table 6. Summary of Past Assessment Methodologies

This figure summarizes the methodologies informing leading biological agent assessments.

ASSESSMENT METHODOLOGIES	AD HOC	CDC	CRS	DHS	EU
Risk Based				●	
Quantitative				●	●
Qualitative	●	●	●		●
Subject Matter Expert Use	●	●		●	●
Transparency			●		
Measure of Confidence					●
Policy Implications			●		●

Biopreparedness strategy assessments, including both risk and impact, or threat, assessment methodologies, inform policy decisions. To assist policy makers the sponsors of these various reports have traditionally offered rank ordered lists or groups which differentiate between levels of potential impact and resource requirements. With the exception of Shea and Gottron (2004), most of the reviewed assessments stop short of

recommending policy objectives. Additionally, past efforts in the field have set a goal to publish updated, reoccurring assessment to stay current with the best available scientific data. However, the methodologies presented above are not generally supportive of reoccurring assessments. Heavy reliance on qualitative studies and data collection through subject matter elicitation make processing changes in data more difficult as assumptions between assessment trials will need to be shared and validated. If the processes and cut-off points used to arrive at conclusions are not adequately described any secondary analysis will struggle in its ability to make a legitimate statement regarding the effect of new information. Without the ability to make meaningful comparisons between past and present conditions, the gains attributed to resource allocation or changes in biopreparedness strategies can not be appreciated or supported.

Problem Statement

The contribution of the research presented above has greatly advanced the field of bio-preparedness in recent years. Yet the result of research utilizing diverse methodologies has lacked a needed consistency for policy makers. Too often the research has been qualitative, subjective, non-transparent, and heavily reliant on subject matter experts as well as intelligence reports of unknown validity. In their report, Shea and Gottron (2004) concede that, "no clear consensus exists with respect to which agents pose the greatest threat," to the Nation. They go on to cite the varied nature of SME opinions with respect to biological weapon use. Explanations for differing opinions include bias, non uniform information access or application to a specific framework that may emphasize different criteria through formulation or weights (Krause, 2008).

Incorporating probabilistic risk-based scenarios like the one performed by DHS, is an attractive option resulting in quantitative solutions. While a step in the right direction, still needing to be overcome are the stepwise assumptions, most commonly informed by SMEs and intelligence estimates, about how an opposition force would operate (NAS, 2007 and Shea and Gottron, 2004). Reliance on a set of contrived scenarios to inform prioritization of resources and preparation activities may only serve to provide a false sense of security (Shea and Gottron, 2004).

Rotz et al. (2002) concluded that their analysis should not be considered definitive and as such continuing evaluations are needed to ensure preparedness of the public health

infrastructure. Biological agents continue to evolve; so too must our knowledge base and analysis methods evolve. Indeed, any methodology used to evaluate these agents should be able to accommodate newly obtained information. Routine assessment cycles for past and future studies would enhance their significance by highlighting information gaps, perhaps leading to research aimed at improving the foundation of knowledge in the field of study. To date, only the Department of Homeland Security has proposed a routine reassessment cycle. Despite this commitment, DHS has been unable to meet scheduled assessment reviews.

The efforts and resultant products of these past assessments have failed to provide a consistent, comprehensive view of potential agent impact based on clearly delineated factors. Nor have they adequately addressed vulnerabilities, limiting their applicability to real world conditions. The purpose of this study was to propose a new methodology for the analysis of biological agents. The end goal will be to provide a rank ordered list of biological agents affecting biopreparedness strategy, based on selected, scientific variables and metrics informed by the literature review. The full spectrum of available data from a thorough literature review was incorporated into the assessment to highlight inherent data gaps and uncertainty. Ultimately, the information gained should serve to assist policy makers in their attempts to distribute finite resources to achieve widespread biosecurity.

Research Objectives and Questions

The objectives for this study were to 1) assess the current status of research relevant to assessing public health impact of biological agents; 2) identify a representative subset of agents of concern for evaluation; 3) identify a minimal set of quantifiable agent characteristics needed to assist with the evaluation; 4) collect data for the chosen metrics, including a range of values demonstrating uncertainty or natural variability 5) develop a mathematical framework facilitating numerical ranking of agents from low to high public health impact; 6) assess public policy implications based on methodology outcomes. Research questions to support these objectives are as follows:

1. What agents should be reviewed in the proposed framework?
2. What variables are pertinent to the assessment of public health impact?

3. How can variables be quantitatively measured?
4. What data is currently available in the literature?
5. How should variables be combined to express a rank ordered list of agents?
6. How do the results of the methodology agree or differ with previous findings?
7. What public policy implication can be drawn from the study?

By completing the objectives and answering the research questions listed above, the present study used, then improved upon the best available research and methods described in the field of study. Agent and variable selection was completed based on a synthesis of past processes to strengthen consistency in the biopreparedness field. Also described in past reports have been variable combinations expressing total potential impact, whether qualitative or quantitative. These reports served as a starting point for formula development; however, by relying on the full range of published, quantifiable data, the proposed methodology progressed beyond prior work in the biopreparedness field. Advancements were made by utilizing referenced data inputs freed from specific, but hypothetical scenarios, and by addressing other previously identified weaknesses within the methodology. Not only did the study address bias, transparency, and uncertainty, but outcomes were comparable to previous findings. Finally, the present study allowed for public policy implications to be both drawn and measured as the systematic approach was conducive to the performance of routine re-evaluations due to changing conditions or information.

Method and Procedures

This study was conducted in five phases 1) literature review; 2) agent/variable selection; 3) data collection; 4) formula development; 5) analysis. Completion of these phases resulted in a systematic approach describing the relative public health impact of the selected bacterial agents based solely on their documented scientific characteristics.

Literature Review

Incorporated in both the planning and execution phase, the foundation of this study was the literature review. In the planning stage the literature review, including past impact assessments, informed agent and variable selection as well as formula development. The literature was used to identify agents of concern and variables of interest that would guide data collection for this study. Despite a broad range of sources, a high degree of commonality was found between both selected bacterial agents and variables of interest in the literature. During the implementation period over 300 references were examined for the purpose of collecting data on the metrics selected for inclusion in the public health impact formula.

The literature search was primarily conducted though online databases. The Lawrence Livermore National Laboratory (LLNL) search engine, SPLASH, was utilized to identify journal articles through its science database. Additional searches at Oregon State University using Academic Search Primer and Google Scholar were conducted to capture as many relevant journal titles as possible. Database searches were conducted systematically by combining the agent name along with key words representing each of the variables/metrics.   In some cases, a lack of literature stifled the data collection process. In these instances leading web-based information centers were elicited to gain insights on reported values and additional reference materials. Past assessments were also reviewed to elicit references that did not surface in database searches.

Agent Selection

The starting point for agent selection was consideration of past work completed by stakeholder agencies. Each reviewed report considered a slightly different list of agents. Annex three to the World Health Organization's 2004 "Public health response to biological and chemical weapons: WHO guidance," details agents chosen for inclusion in

seven separate evaluations. Using the WHO's meta-analysis, agents were chosen for this study if they appeared in three of seven reports. This level of agreement was taken as sufficient concern of potential impacts from an outbreak should one occur. The chosen approach was consistent with several of the assessments outlined in the literature review which tended to select agents based on previous reports. Of these reports the Centers for Disease Control and Prevention prioritization of category A, B and C agents has been recognized as the most widely cited (Tegnell et al., 2006). It should be noted that the CDC publication itself relied on a meta-analysis of past evaluations or select agent lists developed by leading agencies (Rotz et al. 2002). Select agent lists refer generally to those agents agreed upon by consensus of subject matter experts to be the most likely agents employed in a bioterrorism incident.

While the above process was the basis of selection, slight modifications were made on occasion. In addition to the agents selected through the method described above, nine more agents were added for various reasons. To expand upon the scope of the agents presented by the WHO, several emerging diseases were included by considering the CDC category B and C agents along with the category A agents presented in Table 7. With the inclusion of category B and C agents, five agents responsible for machupo, Marburg, psittacosis, Japanese encephalitis and Western equine encephalitis diseases then met the threshold for inclusion in the present study. Influenza also met the criteria for inclusion based on the expanded CDC list, however due to the variability of the influenza strain only the H5N1 strain was chosen for further examination. Viral agents responsible for the Hendra and Nipah diseases were also chosen for inclusion based on their emerging potential to cause diseases. Only recently characterized, these agents have been placed on select agent lists by the Australia Group and CDC (Australia Group, 2006 and Rotz et al., 2002). The final agent added to the assessment was rabies, which was selected for this study as a calibration measure used in the same manner as in the European Commission's threat matrix. Once infected with rabies an individual can expect to live with prompt treatment, however, if symptoms occur before treatment is received, death is almost a certain prognosis (Center for Food Security and Public Health, 2009). With medical advances there have been a few survivors of the virus after even after becoming symptomatic, though these individuals usually experience severe morbidity.

Table 7. World Health Organization Select Agent Comparison

This figure summarizes which agents have been singled out in previous assessments and threat lists by governmental agencies and non-governmental organizations (NGOs).

Biological agent and WHO alphanumeric code for the disease[a] it can cause	United Nations[b] (1969)	WHO[c] (1970)	BWC[d] CBM-F (1992)	Australia Group[e] (1992)	NATO[f] (1996)	CDC[g] category A (2000)	BWC[h]draft Protocol (2001)
BACTERIA (including RICKETTSIA and CHLAMYDIA)							
Bacillus anthracis, A22 (anthrax)	X	X	X	X	X	X	X
Bartonella quintana A79.0 (trench fever)				X			
Brucella species, A23 (brucellosis)	X	X	X	X	X		X
Burkholderia mallei, A24.0 (glanders)	X	X	X	X			X
Burkholderia pseudomallei, A24 (melioidosis)	X	X	X	X	X		X
Franciscella tularensis, A21 (tularaemia)	X	X	X	X	X	X	X
Salmonella typhi, A01.0 (typhoid fever)	X	X		X	X		
Shigella species, A03 (shigellosis)	X				X		
Vibrio cholerae, A00 (cholera)	X	X		X	X		
Yersinia pestis, A20 (plague)	X	X	X	X	X	X	X
Coxiella burnetii, A78 (Q fever)	X	X	X	X	X		X
Orientia tsutsugamushi, A75.3 (scrub typhus)					X		
Rickettsia prowazekii, A75 (typhus fever)	X		X	X	X		X
Rickettsia rickettsii, A77.0 (Rocky Mountain spotted fever)	X	X		X	X		X
Chlamydia psittaci, A70 (psittacosis)	X				X		
FUNGI							
Coccidioides immitis, B38 (coccidioidomycosis)	X	X			X		
VIRUSES							
Hantaan/Korean haemorrhagic fever, etc., A98.5		X		X	X		
Sin nombre, J12.8							X
Crimean-Congo haemorrhagic fever A98.0		X		X	X		X
Rift Valley fever, A92.4		X		X	X		X
Ebola virus disease, A98.3				X	X	X	X
Junin haemorrhagic fever, A96.0 (Argentine haemorrhagic fever)				X	X	X	X
Machupo haemorrhagic fever, A96.1 (Bolivian haemorrhagic fever)				X	X		X
Lassa fever, A96.2				X	X	X	X
Tick-borne encephalitis/Russian spring–summer encephalitis, A84.0/ A84	X	X		X	X		X
Dengue, A90/91	X	X		X	X		
Yellow fever, A95	X	X		X	X		X
Omsk haemorrhagic fever, A98.1					X		
Japanese encephalitis, A83.0		X		X			
Western equine encephalomyelitis, A83.1		X		X			X
Eastern equine encephalomyelitis, A83.2	X	X		X	X		X
Chikungunya virus disease, A92.0	X	X		X	X		
O'nyong-nyong, A92.1		X					
Venezuelan equine encephalitis, A92.2	X	X	X	X	X		X
Variola major, B03 (smallpox)	X	X		X	X	X	X
Monkeypox, B04				X			X
White pox (a variant of variola virus)				X			
Influenza, J10, 11	X	X			X		
PROTOZOA							
Naeglaeria fowleri, B60.2 (naegleriasis)							X
Toxoplasma gondii, B58 (toxoplasmosis)		X					
Schistosoma species, B65 (schistosomiasis)		X					

Notes

[a] Diseases are identified by the alphanumeric code assigned by the WHO International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10).

[b] United Nations, Chemical and bacteriological (biological) weapons and the effects of their possible use: Report of the Secretary-General, New York, 1969.

[c] World Health Organization, Health aspects of chemical and biological weapons: Report of a WHO group of consultants, Geneva, 1970.

[d] UN Office of Disarmament Affairs, compilation of declarations of information by BWC States Parties in accordance with the extended confidence-building measures agreed at the Third Review Conference, DDA/4-92/BW3 plus Add.1, Add.2 and Add.3, data from Section 2, Past offensive biological R&D programmes, of Form F as filed by Canada, France, Russian Federation, UK, and USA in 1992.

[e] Australia Group document AG/Dec92/BW/Chair/30 dated June 1992.

[f] NATO Handbook on the Medical Aspects of NBC Defensive Operations, AmedP-6(B), Part II – Biological, 1996.

[g] Centers for Disease Control and Prevention: Biological and Chemical Terrorism: Strategic Plan for Preparedness and Response. Recommendations of the CDC Strategic Planning Workgroup. Morbidity and Mortality Weekly Report, 2000; 49 (No.RR-4):1–14.

[h] Ad Hoc Group of the States Parties to the Convention on the Prohibition, Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction, document BWC/ AD HOC GROUP/56-2, at pp 465-466, which is in Annex A of the Chairman's Composite Text for the BWC Protocol.

Lastly, one agent was left out of the analysis. An error in the transfer of information between documents resulted in the agent causing Crimean-Congo hemorrhagic fever to not be identified as meeting the threshold criteria as laid out above. Only after the data

collection phase was completed did this error come to light.   In the end 33 agents (Table 8) were carried forward throughout the assessment.

Table 8. Public Health Impact Assessment: List of Agents and Associated Diseases
The above table summarizes, by category, those agents selected for evaluation in this study.

AGENT	DISEASE
Bacteria	
Bacillus anthracis	Anthrax
Brucella species	Brucellosis
Burkholderia mallei	Glanders
Burkholderia pseudomallei	Melioidosis
Chlamydia psittaci	Psittacosis
Coxiella burnetii	Q fever
Francisella tularensis	Tularemia
Rickettsia prowazekii	Typhus fever
Rickettsia rickettsii	Rocky Mountain spotted fever
Salmonella typhi	Tyhoid fever
Salmonellosis	Salmonella
Shigella species	Shigellosis
Vibrio cholerae	Cholera
Virus	
Alphavirus	Chikungunya viral fever
Alphavirus	Eastern equine encephalitis
Alphavirus	Venezuelan equine encephalitis
Alphavirus	Western equine encephalomyelitis
Arenavirus	Junin hemorrhagic fever
Arenavirus	Lassa fever
Arenavirus	Machupo
Filovirus	Ebola
Filovirus	Marburg

Flavivirus	Dengue fever
Flavivirus	Japanese encephalitis
Flavivirus	Yellow fever
Flavivrus	Tick-borne encephalitis
Influenza virus, H5N1	Avian influenza
Lyssavirus	Rabies
Paramyxoviridae	Hendra
Paramyxoviridae	Nipah
Phlebovirus Bunyaviridae	Rift Valley fever
Variola major	Smallpox

Table 8 (Continued). Public Health Impact Assessment: List of Agents and Associated Diseases. The table summarizes, by category, those agents selected for evaluation in this study.

Variable Selection

The public health impact of an agent is primarily determined according to is mortality and, to a lesser extent, morbidity statistics. However, before an agent reaches the stage of causing either of these significant endpoints there are several characteristics, or variables, which influence the outcome of a specific agent. As with agent selection the literature review of previous efforts showed a high degree of consistency with respect to variable selection. Many variables of interest were considered, but only those variables that could be tied to a specific agent and could be quantified were chosen for further development in this study. Despite consistency, variables described in the literature review were often termed as broad categories such as availability or production without a specific definition. Variables may be described in many ways depending on the choice of metric, or quantifiable measurement. To move beyond the generalities of pervious studies, the next step was to define metrics that accurately described variables of interest in a quantitative manner.   In all 10 variable categories were chosen to describe outbreak potential of a specific agent from acquisition through disease manifestation to the endpoint consequence (recovery, lasting morbidity, death). From the 10 categories, 13

metrics were developed to assess each variable. Table 9 lists chosen variables and their associated metrics. A short description of each of the variable is described below. Appendix A outlines in greater detail the definitions, description, and the range of possible values for the metrics listed in Table 9.

Table 9. Public Health Impact Assessment: List of Variables and Associated Metrics

This table outlines the variables, associated metrics and realized data ranges included in the evaluation.

VARIABLE	METRIC	DATA RANGE
Availability	1. Number of continents where agent is endemic	0-6 continents
	2. Number of years since last case, worldwide	1-30 years
Production	1. Required growth technology	1-4 difficulty ranking
	2. Maximum recorded concentration per milliliter	6.6×10^5 PFU/ml- 2×10^{10} CFU/ml
	3. Measured or estimated infectious dose (ID_{50})	$1-10^{11}$ organisms
Routes of Infection	1. Number of routes of infection	1-3 routes
Stability	1. One minus decay (%) per minute	0-98.33% per minute
Person-to-Person Transmission	1. Number of subsequent infections caused by an initial case (R_0)	0-38 cases
Incubation Period	1. Time between infection and expression of symptoms	0.125-10,585 days
Morbidity	1. Percentage of the population who experience a persistent state of ill health	0-70%

Mortality, Untreated	1. Percentage of the population who would die without treatment	0-100%
Mortality, Treated	1. Percentage of the population who die from the disease after treatment	0-100%
Treatment Efficacy	1. Percentage of the population for which a treatment prevents mortality as an outcome	0-97%

Table 9 (Continued). Public Health Impact Assessment: List of Variables and Associated Metrics. This table outlines the variables, associated metrics and realized data ranges included in the evaluation.

Availability

Availability measures the presence of the agent or disease. Shea and Gottron describe natural prevalence of an agent as one of the most important criteria to consider when describing potential outbreak impacts (2004). For this study two metric categories were used to describe availability. The first metric focused on geographic range while the second metric considered the reported frequency of disease. Geographic range was illustrated by the number of continents (excluding Antarctica) in which the agent is endemic in the human population, zoonotic reservoirs or is present in environmental media (soil, water). The agent was deemed endemic if it is either always present or occurs on a regular, anticipated basis such as the seasonal influenza virus. The second metric measured the number of years since the presence of the disease caused by an agent of interest was reported in the online database ProMed-mail. ProMed-mail, sponsored by the International Society for Infectious Diseases, allows international medical personnel, public health officials and researchers to post notifications of disease cases/outbreaks as confirmed through the host nation's laboratory system. Research for each of the agents was collected over a year long period between the summer of 2007 and the summer of 2008. To minimize seasonal variance a single reference date of August 27, 2007 was used throughout the analysis regardless of when the research was actually conducted. The first recorded outbreak in either the animal or human population prior to August 27, 2007 was noted and recorded in one year intervals. A one year timeframe was specified

to reduce, once again, seasonal bias for those agents that are expressed during select timeframes. Highly prevalent agents increased the expected public health impact.

Production

Like availability, multiple metrics were developed to fully describe agent production. While the overall objective of this assessment is to rank the public health impact of either a natural or man-made outbreak, the production variable is most aptly applied to man-made outbreaks. Despite this, it may be possible for ease of human production to relate to ease of natural production through replication potential. The first factor considered was a categorical description of the media required to grow an agent. Examples of media included broth, small or large animals, and cell culture processes. Lower technology requirements for replication infers lower barriers to man-made production and hence a greater likelihood of use by the widest population. With respect to this inverse relationship, larger values were assigned to simple technologies. Each media category metric was subsequently assigned a specific value for inclusion in the quantitative evaluation.

The second metric recorded maximum concentration as reported in journal articles. The unit of measurement was colony forming units per milliliter (CFU/ml) for bacteria agents and plaque forming units per milliliter (PFU/ml) for virus agents. For consistency within the variable, maximum concentrations were related to the simplest growth media expressed in the first metric. The last metric used to describe the production variable was the infectious dose required to infect fifty percent of the population (ID_{50}). Infectious dose itself is not traditionally included as a factor of production. However, in this assessment ID_{50} was divided into the highest reported concentration to arrive at the maximum number of doses produced by the simplest production technology. High dose per concentration ratio was indicative of higher public health impact.

Routes of Infection

Routes of infection are pathways by which the agent has been known to infect humans and cause disease. Some agents may manifest with different symptoms and severity depending on the route of infection (Inglesby et al., 1999). For the purposes of

this analysis, three pathways were considered: inhalational, ingestion and direct contact. Inhalation involves the intake of aerosolized particles through the respiratory system while ingestion involves the oral intake of an agent by itself or in combination with food or water. Direct contact encompasses differing aspects of dermal contact, including bite transmission, entry through skin abrasions/openings, mucus membranes or sexual contact. The metric used to assess this variable was the number of significant routes in which an agent was able to cause infection leading to disease manifestation. Furthermore, to maintain consistency throughout the assessment, ID_{50} and mortality estimates were tied to the primary, or typical, route of infection whenever available data permitted. Increases in expected public health impact would result from a greater number of possible routes of infection.

Stability

Environmental stability was derived from reports of biological or physical decay found in the literature. With biological decay, the organism may still be present, but lacking capacity for infectivity or replication. Physical decay describes the complete removal of the organism. Measure of decay were not consistently described in the literature; however, percent decay per minute was the predominate measure and has been carried over to this assessment. Decay itself was not incorporated into the assessment. Rather stability, the opposite of decay, evaluated as one minus decay was used. Stability increases suitability for storage and dissemination after production. Higher stability rates result in greater public health impacts.

Person-to-Person Transmission

Person-to-person transmission (R_0) is a determining factor in the extent of and speed at which an outbreak spreads through a population. R_0, defined as the number of secondary cases caused by immediate contact with an initial case, is a common measure of transmissibility. Person-to-person transmission can test public health protective measures and complicate treatment regimens, in addition to being resource intensive.

The R_0 value was incorporated in the assessment to highlight these considerations. The higher the R_0 value, the higher the expected public health impact.

Incubation Period

The metric chosen for incubation period was the time, in days, between infection by an agent and first expression of clinical symptoms. The quick onset of symptoms minimizes opportunities for individuals to seek medical treatment and receive effective countermeasures, which may alter morbidity and mortality endpoints. Shorter incubation periods lead to higher public health impacts.

Chronic Morbidity

Morbidity describes a state of ill health (Rossignol, 2007). The metric chosen to illustrate morbidity was the percentage of the infected population who survives, but experiences a persistent state of ill health for at least one year (chronic) past the acute stage of disease. Only severe morbidity, affecting normal daily life was considered in this assessment. Key indicators indicative of morbidity in the literature included neurological impairment, inability to independently function, blindness, deafness and amputation. High public health consequences stemmed from elevated morbidity levels.

Mortality, Untreated

Untreated mortality was defined as the percentage of the population who would die as a normal outcome of disease if treatment was either not provided or not available. Consistent with past assessments, high untreated mortality was directly related to high public health impact.

Mortality, Treated

Treated mortality was expressed by one of two measures. As traditionally reported, treated mortality reflects the percentage of the population who die as a result of the disease caused by an agent, despite receiving treatment. In the reviewed literature, treated mortality was often provided without clarification of the treatment received. This

fact confounded comparison of treatment survival rates as it remained unclear if all populations from developed and developing countries received the best available medical countermeasures.

The second measure of treated mortality was derived from available treatment efficacies. While attempts were made to differentiate pre- and post-exposure vaccines and drug therapies, in the end insufficient data hampered this process. There was a distinct lack of uniform data on both pre- and post-exposure treatment options as well as their associated efficacies. Publications rarely reported human trials for experimental vaccines or drug therapies; instead, differing animal models were relied upon to infer efficacies. Given the complexity of relating animal models to expected human results, only field tested countermeasures or data from human trials were considered in this assessment. In order to capture all relevant information, a metric was developed by examining optimal efficacies of all currently available treatment options. In this manner the cumulative medical countermeasures represented the best case scenario for received treatment. Theoretical treated mortality was then calculated as untreated mortality multiplied by the efficacy of optimal treatment. For the purposes of this assessment, the lower of the treated mortality metrics, either as reported or as theoretically derived, was carried forward in the calculation of the public health impact score. As with untreated mortality, high treated mortality was directly tied to a higher public health burden.

Data Collection

Data collection parameters were defined by the variables and subsequent metrics chosen to fully describe the factors that contribute to the public health impact experienced by the population. On one hand, a paucity of data hampered data collection for some agents and/or metrics while on the other hand a great range of data was identified for other agents and/or metrics. To provide a robust assessment methodology as devoid of bias as possible, it was necessary to conduct a detailed literature search on each agent. Information about the characteristics of an agent was gathered from the literature search and entered onto individual evaluation sheets initiated for each agent. Each sheet summarized the range of available information about the scientific characteristics specific to each of the agents. First order references were used whenever

possible to cite entries onto the evaluation sheets. Summary sheets containing the low, high and most likely values for all agents were developed from the individual evaluation sheets. Data from the summary sheets was transferred to an excel file for normalization treatment and incorporation into the public health impact formulas.

Data Ranges

The product of each literature search on a particular agent resulted in the development of individual evaluation sheets which captured the full spectrum, by metric category, of data found in journal articles and online databases. By recording the range of data values it was possible to see the level of agreement, or lack there of, in the scientific community. A range of values was collected for several metrics including:

1. Stability
2. Infectious Dose (ID_{50})
3. Incubation Period
4. Person to Person Transmission (R_0)
5. Morbidity
6. Untreated Mortality
7. Optimal Treatment Efficacy
8. Treated Mortality

Three data points for each quantitative metric were transferred from the individual information sheet to the collective summary sheet for all biological agents (Appendix B). These points represented the lowest, highest, and most likely reported value found in journal literature or reputable databases. Low and high data points were directly transcribed from the minimum and maximum values reported in the literature. Determination of the most likely value was made in one of two ways. The first method was used when the preponderance of evidence in the literature strongly supported a specific value. In this case the mostly likely value was obtained by taking the single value or average of a small, commonly cited, spread of values. In situations where the literature references were highly variable with little agreement among values, the most likely value was calculated by taking the average value between the lowest and highest data points.

Missing Data and Limited Data

Missing data hampered the data collection. In some cases either no data was available or only a single data point was identified. If no value for a particular metric could be identified after exhausting all database and journal queries, the entry for that metric, specific to a particular agent, was left blank. When data collection for all biological agents concluded, missing values for a metrics were derived from the lowest, highest, and most likely values that were found among all agents with reported values within its class of biological agents (bacterial or viral). In this manner both the best case (low impact) and worst case (high impact) scenario was included as a possible outcome. Most likely values for missing data were calculated by taking the average of all known most likely values for other intra-group agents (bacterial or viral). As with the range of values described above, missing data was another indicator of the level of uncertainty surrounding the impact of a specific agent. When only one reference could be found to provide a single data point for a metric, the same value was used for all three data positions (low, high, most likely).

Uncertainty

Incorporation of uncertainty has rarely been addressed in past bioassessment work (Tegnell et al., 2006). A priority of this assessment was the internalization of uncertainty making it an integral part of this analysis. As addressed above, by capturing the range of available data or by inferring a range of possible values in those instances with data gaps, the level of uncertainty is preserved throughout the analysis. A single value for all three data points can not be displayed as a range of uncertainty; however, it should be noted that one identifiable value is not necessarily any more reliable than unknown inputs. Both outcomes signify needed areas of research for further development of the field.

Formula Development

The final stage of this study was the development of two mathematical formulas capable of combining collected variable/metric data inputs in order to derive numerical value expressing an agent's untreated and treated public health impact. The result of

each formula was a public health impact score. The development of this score supported a quantitative ranking of public health impact posed by any agent, relative to the evaluated group. Current guidelines on formula development of this nature exist do not exist. However, processes developed to express public health impact in past assessments informed the current effort.

Public health impact formulas developed in the present assessment incorporated variables significant to the acquisition, infection and expression of the disease into a core formula. Within the core formula itself several of the metrics were combined to form a general expression of the variables which comprised the core formula. An availability term was formed from the product of endemic geographic range and frequency of disease. The production variable included in the core formula was the product of the required growth technology and the maximum number of infective doses where infective dose was calculated by dividing the reported production concentration by the recorded ID_{50}. All other variables were represented by a single metric individually added to the core formula:

$$Core\ Formula = Availability + Production + Stability + Routes\ of\ Infection +$$
$$Person\text{-}to\text{-}Person\ Transmission + Incubation$$

Before adding each variable component together a normalization formula was applied to scale each value from zero to one. This procedure was incorporated in order to ensure inputs had the same potential to contribute to the core score. Normalization was performed through one of two different methods. In situations where a higher value represented higher consequence to public health the normalization formula applied was the directly proportional impact formula. When lower data points signified higher public health impact the indirectly proportional impact formula was applied:

Directly Proportional Impact Formula = (Data Point - Minimum Value) / (Maximum Value - Minimum Value)

Indirectly Proportional Impact Formula = 1 - ((Data Point - Minimum Value) / (Maximum Value - Minimum Value))

Differentiating the core formula were the chief endpoints, namely morbidity, untreated mortality and treated mortality. The core formula was multiplied by the endpoint consequences caused by a particular agent in order to emphasize the legacy of each agent. For example an agent may have a high core formula score, but have little to no significant expression of morbidity or mortality. In situations of this nature there would be little resultant public health impact to consider unless changes were realized in the endpoint consequences. Indeed this was the case for agents causing Lassa, Junin hemorrhagic fever, psittacosis and Q-fever. These diseases had high core formula impact scores, but due to low morbidity and mortality rates they end up at the bottom of the rankings in the final outcome.

Untreated Public Health Impact Formula =

Untreated Public Health Impact Score = *Core Formula* $\times$ [(Morbidity + Untreated Mortality) ∕ 2]

Treated Public Health Impact Formula =

A. Treated Public Health Impact Score = *Core Formula* $\times$ [(Morbidity + (Untreated Mortality $\times$ (1-Optimal Treatment))) / 2]

B. Treated Public Health Impact Score = *Core Formula* $\times$ [(Morbidity + Treated Mortality) ∕ 2]

Untreated public health impact scores were calculated when the core formula was multiplied by a complex of morbidity and untreated mortality endpoints. To express treated public health impact, two formula options were developed to account for

differences in how treated mortality was reported in the available literature. The first method was a direct measure of treated mortality as reported by case fatality ratios after treatment was received. The second method indirectly stated mortality through the efficacy of available treatment options. However, it could often not be explicitly identified if patients received optimal or even equal treatments. As a result treated mortality estimates and efficacies were difficult to compare at best. Both case fatality estimates and efficacy values were calculated in the data analysis process; however, only the value representing the lowest public health impact was incorporated into the treated public health impact formula. By choosing the lower of the two values to represent treated impact, the assessment represented the optimal outcome supported by the literature. Morbidity values remained the same in both the untreated and treated impact formula.

Variable Weights

An objective of this assessment was to maintain an unbiased approach in order to be flexible to varying outbreak circumstances. Depending on the characteristics of an outbreak, certain variables may play more significant roles than other variables. The European Commission's threat matrix included unspecified variable weights and repetition of variables deemed to be of greater importance than others as determined by subject matter experts (Tegnell et al., 2006). However, the majority of past bioassessment work have left out variable weights in their scoring systems (Krause, 2008). In order to maintain an unbiased approach and remain open to changing outbreak considerations the public health impact formulas expressed the combination of metrics with simplicity and without additional weights.

Calibration

Provided, the developed formulas adequately represent those factors contributing to public health impact, calibration agents should be ranked relative to expected outcomes after all processes were applied. Like the European Commission's efforts on its threat matrix, the formulas expressed above were also calibrated using the agents that have a

near 100% mortality rate or practically 0% treated mortality rate. For example, using untreated mortality data, agents causing anthrax, plague, and rabies are experienced in the population at up to 100% mortality rates on the high end of the data range. At the same time *Alphaviruses* causing Chikungunya fever and Venezuelan equine encephalitis as well as the bacterial *Salmonella* all result in near 0% mortality rates, even when untreated. Calibration agents rank as expected as seen in the next section.

Results

Computation of the public health impact score was accomplished for three specific groups of agents. The first two sets of results were for the separate categories of bacteria and viral agents. Public health and research facilities often divide bacterial and viral departments and hence research priorities. For this reason it was important to consider both bacteria and viral agents individually. Agents in these individual groups were also combined, the third group for which results were calculated, in order to understand the relative threat posed by the separate categories of biological agents.
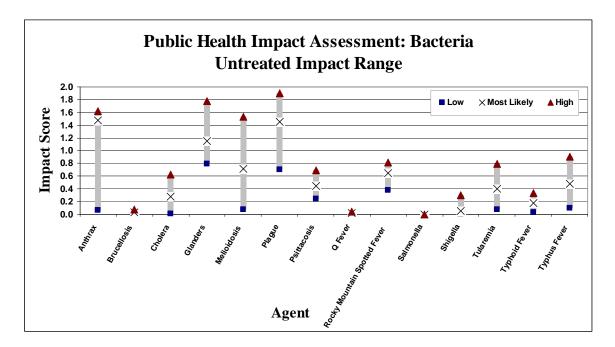
Bacteria Agents

Figure 1. Public Health Impact Assessment, Bacterial Agents Untreated Range

This figure depicts the range of potential public health impacts of bacterial agents given all available data.

Fourteen bacterial agents were evaluated in this research effort. Untreated public health impact for these bacterial agents was first considered. Those agents that result in anthrax, glanders and plague consistently placed as the top three impacts agents across

the considered spectrum. Anthrax and plague are commonly cited in past assessments where as glanders has only gained significant consideration in small-scale evaluations (Shea and Gottron, 2004). After optimal treatment is applied and treated mortality is combined with the core public health impact formula, the overall impact score was reduced, as expected given treatment. High and most likely impact rankings remained relatively consistent with the rank ordering of the untreated results. For low impact ranges, Rocky Mountain spotted fever displayed a higher relative level of potential harm than other, better known agents and their associated disease outcomes.
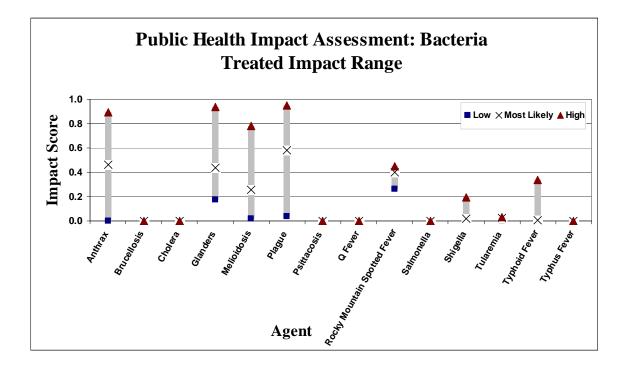

Figure 2. Public Health Impact Assessment, Bacterial Agents Treated Range
This figure depicts the range of potential public health impacts, given all available data, after treatment.

The result of incorporating a range of inputs from low to high impact was immediately apparent in Figures 1 and 2. Illustrated was the possible range of scores that could be derived for any particular agent depending on the input provided. Here the spectrum of data was derived from the literature; however, given the results, it is possible to draw parallels to the difference of opinion among subject matter experts. For example,

anthrax, whose score for high and most likely impact outcomes was the top tier, dropped to the bottom of the rank order list when the low range of data was considered. At the same time lesser known agents responsible for glanders and Rocky Mountain spotted fever climbed in importance when data on the lower end of the spectrum was taken into account. With the incorporation of published data ranges, it becomes possible to account for the span of results expressed in the past assessments. In short, the outcome depends not only on the formula used to arrive at the results, but chiefly on the data inputs applied.

The application of the public health impact formula to bacterial agents was generally consistent with the varying outcomes of past assessments. Significant variability in input values has a quantifiable effect on the results achieved. For example, plague can rank at the top of the list for high and most likely treated impact, but have negligible impact at the low end of its potential range. These results signify the importance of maintaining transparency in both the process and in the inputs used for future assessments.

Virus Agents

Nineteen viral agents were included in this study. As with the bacterial agents the range of potential public health burden from low to high impact is delineated in both Figures 3 and 4. Due to its high level of mortality and morbidity, the agent responsible for rabies disease represents the top agent of concern across all impact levels. In addition to rabies, agents causing Japanese encephalitis and Eastern equine encephalitis consistently resulted in elevated public health impact. One of the best known viral agents, *Variola major* (smallpox), which places highly in previous assessments, only scored in the top tier of the present assessment when the high range of data was considered. It should be noted that prior to eradication, smallpox was experienced with endemic frequency in certain areas, which is not reflected in the availability metrics for this assessment.

The inclusion of treated mortality into this public health assessment resulted in more variable outcomes than experienced with bacteria. Eastern equine encephalitis was shown to score in the top three ranks among all impact categories. Rounding out the top three agents across low, high and most likely impacts were smallpox, Japanese

encephalitis, rabies, Ebola and Hendra. Top ranking viral agents in the present assessment again incorporate high ranking agents from previous assessments while at the same time highlighting the potential impact of lesser known, emerging agents such as those causing Eastern equine encephalitis and Hendra.
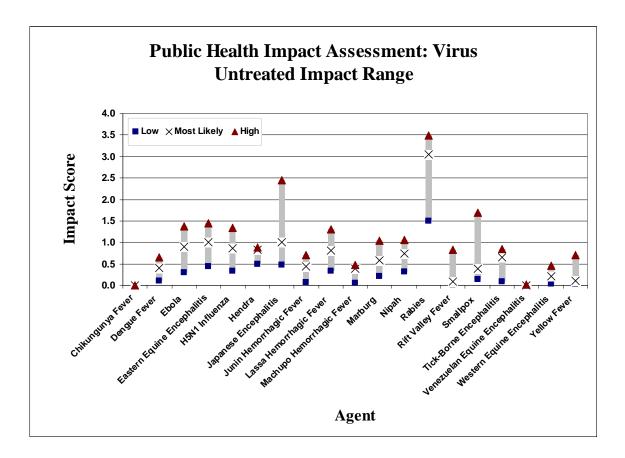

Figure 3. Public Health Impact Assessment, Viral Agents Untreated Range

This figure depicts the range of potential public health impacts of viral agents given all available data.
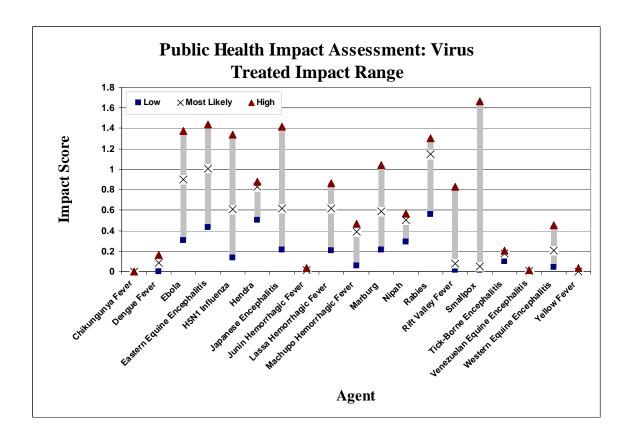
Figure 4. Public Health Impact Assessment, Viral Agents Treated Range

This figure depicts the range of potential public health impacts caused by viral agents, given all available data, after treatment.

Combined Agents

While it is important to understand the ranking of bacteria and viruses separately, it is also essential to understand the relative ranking of all agents examined in this study. In order to prioritize research and funding, a complete view of biological agents requires an integrated view of the potential impacts caused by both bacterial and viral agents.
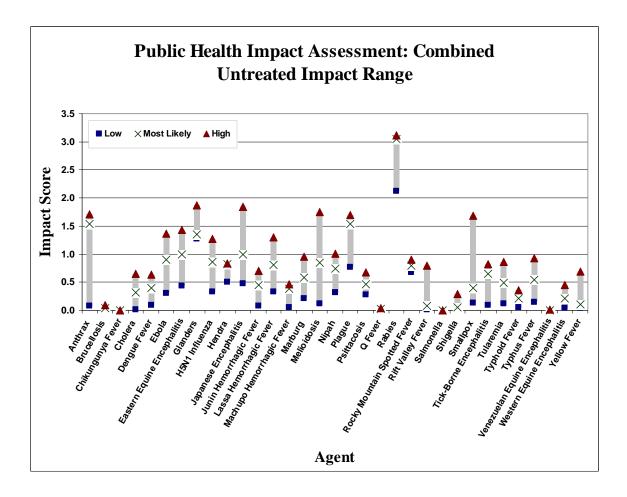
Figure 5. Public Health Impact Assessment, Total Untreated Impact Range

This figure depicts the range of potential public health impacts of all agents, given all available information.

At the high end of combined, untreated public health impact, the top three agents were represented by the diseases known as rabies, glanders and Japanese equine encephalitis, each of which scored highly when separate analyses was performed. Viral agents tended to score higher than bacterial agents when considering the high range of morbidity and untreated morality. Bacterial agents were more commonly found in the top ranks when most likely and low end spectrum impacts were weighed. The top three agents in the mostly likely impact range are expressed as rabies, plague and anthrax disease. Using the data at the low end of impact range rabies, glanders and plague end up as the agents with the highest, relative consequence. With the exception of rabies and

Japanese equine encephalitis the relative outcomes reflect those of past assessments presented in the literature review. It should be noted that rabies has not traditionally been selected as an agent evaluated in past assessments; therefore comparisons can not be made as to the significance of this result.
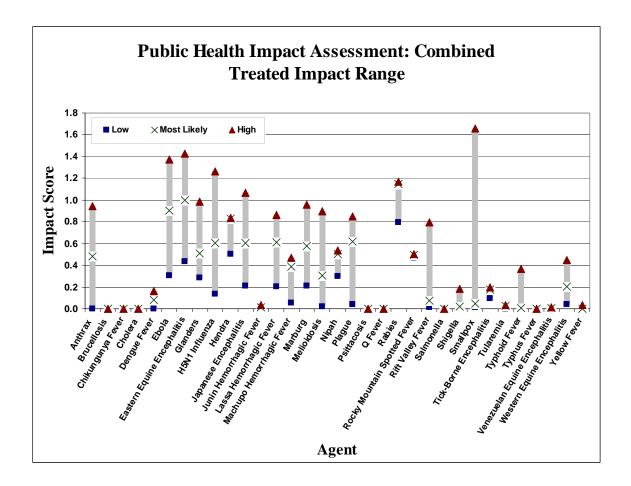

Figure 6. Public Health Impact Assessment, Total Treated Impact Range
This figure depicts the range of potential public health impacts of all agents, after treatment, given all available information.

In the application of untreated mortality combined with the core formula, both bacteria and virus agents were represented across all impact ranges. Once optimal treatment outcomes were applied to the core formula, results shifted to display the higher potential consequences of viruses compared to bacteria. The viral agents responsible for

smallpox, Eastern equine encephalitis and Ebola were the top three scoring agents on the highest end of the spectrum. Assessing data on the low end of the spectrum resulted in viral diseases including rabies and Hendra as well as the bacterial agent causing Rocky Mountain spotted fever scoring in the top three positions. At the same time the most likely range of data portrays viral agents causing rabies, Eastern equine encephalitis and Ebola as the top three high consequence diseases in this category.

In the combined assessment, a mix of bacteria and virus agents result in the diseases with the highest potential public health consequence when untreated mortality is specified. However, when effective medical countermeasures were analyzed, viral agents predominantly scored higher than bacterial agents. The result obtained here could be indicative of a disparity of treatment options between bacteria and viruses.

Discussion

Significance of the Study

A reoccurring limitation in previous studies has been the reliance on qualitative techniques, often resulting in differing outcomes. Without a formal process in place to explain criteria and cut-off values, subject matter expert informed qualitative studies can not be replicated. Nor can a meaningful comparison be made if modification of metrics such as treatment efficacy or mortality rates warrant revision of an agent's impact on public health. The current methodology has addressed the vulnerabilities of previous assessments to advance the status of the field.

Independent of the findings in this study, a key strength of this report was the commitment to a quantitative methodology. Except for the inclusion of emerging biological agents, the process relied largely on the traditions in the field when it came to agent and variable selection. Metrics were chosen not only for their suitability to describe variables integral to the process of infection and its outcomes, but also for their ability to be quantitatively defined. By focusing on acquisition of published data versus subject matter expert elicitation, bias was minimized while transparency and information reliability were increased. Compared to qualitative methods, outcome ambiguity was lessened with the application of these quantitative measures.

The level of uncertainty was addressed in several ways. First by not hinging the analysis on a particular scenario the results were not confined to a set of arbitrary parameters and thus remain flexible to adapt to real world conditions. Secondly, the level of knowledge in the field was assessed by the range, or lack there of, of data as identified with the three data points of interest (low, most likely, high) along the spectrum of all available inputs. In instances where data was missing the range of possible outcomes was used to minimize uncertainty given high likelihood that the actual value laid within the spread of data. Rankings from low to high potential impact varied with the incorporation of data ranges. The outcome highlights the importance of inputs to any biological assessment making comparisons between agents. By examining the spectrum of data it was possible to legitimize the disparate findings of past assessments that have been informed by different subject matter experts, utilizing nontransparent methods.

Public health impact scores were formulated as a function of quantifiable data inputs, resulting in an ordered numerical ranking of the biological agents according to their relative impact. Beyond a prioritization scheme implied by ranking agents, this assessment can also be useful in policy development related to bioterrorism preparedness. The formula provided contains variables with equal weights, which enables the formula to be adaptable to both circumstances and priorities. This feature would allow different agencies involved in specific facets of biopreparedness to emphasize their own areas of concern. With raw data provided as inputs, it would then be possible for agencies to alter the formula to seek an outcome specific to their interests.

As knowledge about epidemiological variables related to both natural outbreaks and intentional attacks become better understood, the formulas could be restated to emphasize significant attributes. Finally, as with the European Commission's threat matrix a calibration tool was used to judge the appropriateness of outcomes. Calibration performance was generally consistent with expected results increasing confidence in formulations derived to achieve public health impact scores.

Policy Implications

Through this assessment a rank ordered list of agents has been developed relative to expected public health impact. The appeal of the rank ordered list was that it can be directly compared to key policy metrics such as level of funding for a specific agent, detection capabilities, or medical countermeasure options. With anticipated impacts identified, policy makers can assess the level of resources currently devoted in segments of the biopreparedness field and make adjustments requisite to associated levels of potential impact. Openly available data enables changes in knowledge levels to be apparent and easily incorporated into subsequent data analysis process. The ability to update the analysis based on newly described data also allows policy makers to measure the effect of their investments through recalculation of the formula and comparison between initial levels of impact and the resultant level of public health impact after changes in resources occur.

Past assessment have not considered separate evaluations of untreated and treated outcomes, instead they have relied on one formula to arrive at their findings. However,

as Figure 7 illustrates, there is all too often little difference between the untreated and treated public health impact scores, especially for viral agents. The main reason that treated impact levels remained the same as the untreated levels during the present analysis was the lack of medical countermeasures including pre- and post-exposure vaccine and/or antimicrobials/antiviral drug therapies. When countermeasures were available, the literature commonly reported multiple treatment options with higher efficacies for bacterial agents compared to viruses. These instances highlight the opportunities to lower public health impact through additional funding or the realignment of fiscal resources.
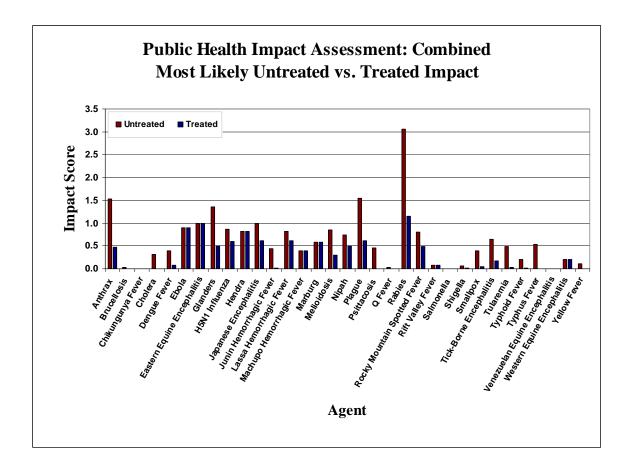

Figure 7. Public Health Impact Assessment, Untreated vs. Treated Mortality

This figure depicts the most likely public health impact values both before (untreated) and after (treated) treatments have been applied.

Limitations of the Study

Improvements notwithstanding, there were also limitations in the present study. While every effort was made to review the pertinent literature forming foundation of the biopreparedness field, it was possible that some relevant studies or journal articles were omitted. For the purposes of this study, data collection was limited to information openly available in the scientific literature. Much of the research related to this topic has been rooted in biologic warfare and biodefense strategies. Largely sponsored by the Department of Defense, this work has generally been classified. By limiting research to publicly available data it is a near certainty that the data collected for the assessment is incomplete in nature.

Despite the comprehensive goal of this method, practicality limited the number of agents reviewed in the assessment. It is entirely possible that agents not described in this assessment pose greater potential impacts to public health than those agents selected given the criterion developed in the procedures and methods and section. The significance of results was limited by the exclusion of Crimean-Congo hemorrhagic fever, which ranked highly in both the CRS report and the Ad Hoc Group's evaluation of biological agents. Crimean-Congo hemorrhagic fever should have been selected for evaluation, but was excluded due to a transfer error from the original document to the author's working agent list. Overall, there existed a general sense of agreement on variable categories integral to infection and disease manifestation. However, not considered in this study is the role of public perception, nor the secondary psychological impacts and economic outcomes that have recently been considered in the area of study (NAS, 2007 and Shea and Gottron, 2004). Heightened public fear may contribute to higher levels of panic with the potential to exponentially increase demand on medical resources as a result of the worried well. While worth exploration in future assessments, a lack of measurable, uniform data made their incorporation into the present study infeasible. In order to capture the changing nature of some agents a variable to measure the propensity of an agent to mutate was pursued, but ultimately left unresolved due to an inability to find a suitable metric. Unfortunately, no commonly available, standard metric could be identified that would allow for incorporation into a quantitative analysis.

Regardless, the ever changing nature of biologic agents makes this variable an important one to consider for future assessments.

Selection of quantifiable metrics was one of the primary methods implemented to reduce bias and uncertainty.   Vulnerabilities such as bias and uncertainty are introduced by the reliance on subject matter experts who have often been called upon to supply judgments used as inputs into the processes of past assessments. However, bias could not be completely removed from the analysis. The determination of source reliability and the appropriateness of the data included in the data summary sheets (Appendix B) are examples of the judgment calls required during the course of this study. To strength the significance of the study, a recommendation for future approaches would be the inclusion of a quantifiable metric capable of capturing the degree of certainty or confidence in the inputs.

The most significant limitation to the present study was the lack of widely available, consistently reported data. While some agents were able to be fully described by the available literature with data inputs for each metric, some agents were poorly understood or described in the literature. Confidence in the findings for under-represented agents is reduced by the number of resultant knowledge gaps. Missing data was mostly commonly found within specific categories such as stability, treated mortality and the reported efficacies of medical countermeasures. The data analysis dealt with missing data by utilizing the spread of data found among all agents for which information was available for a specific metric. Given the large spread of data one can be fairly confident that the true and, as of yet unknown, value lies somewhere within the assigned range. Perhaps more troubling than the missing data were the instances in which only one value was cited. Under these circumstances a metric was fully described by only one study, without the ability to assess confidence in its findings.

With only minimal formula guidance the methodology relied mainly on the approaches of past assessments which have concentrated on combining selected variables of interest. The presented public health impact formulas maintained this approach by adding equally weighted variables in its core formula that was then multiplied by chosen outcome consequences. Epidemiological knowledge may later determine that the method underestimated or overvalued certain variables represented in the formula. Calculation of

public health impact scores, allowed for meaningful rankings to be made within the selected group of agents. Using the normalization process ensured all variables were equally represented, but it meant that a raw score was not carried forward throughout the assessment. Therefore the outcomes were only valid relative to the other agents within the current study and can not be directly transferred to other analytical processes. In addition, the metrics selected to provide data inputs did not represent normally distributed data, but rather discrete values. The result was a lack of statistical power significantly limiting analytical decisions on many aspects of the assessment to include formula development and visual display of the outcomes.

Recommendations

In the literature review, critiques of past assessments commonly included a lack of:

1. data transparency
2. representative data or subject matter experts
3. qualitative processes
4. consideration of uncertainty

The method presented in this study has attempted to address these concerns and advance the field of biopreparedness as a result. Despite any progress that has been achieved, there still remains considerable room for the expansion of this field. Recommendations for methodological improvements rest largely with the opportunities noted in the previous section.

In their publication, Rotz et al., noted the potential power of health impact or threat assessments as decision making tools (2002). At the same time, they noted the importance of standardization in assessments in order to increase their usefulness as prioritization aids. The process developed in this effort built on, but differed from past assessments methods. As previously stated, there are no guidelines for the advancement of a single formula with agreed upon variable/metric inputs to describe potential impact, or threat, to a population as a result of an outbreak from a biologic agent. Without shared data and consistent formulations the resultant outcomes will continue to differ. Disjoint findings will continue to confuse policy makers and frustrate a strategic approach to biopreparedness. The field would benefit from a joint commission, across academic

disciplines, focusing on agreement of variables and formulations. This information could then be used by researchers and government agencies alike to assess potential impact. An effort of this nature should broaden the current scope of the field to include psychological, economic and mutation factors not traditionally included in previous assessments. Given agreed upon quantifiable metrics and formulations, future research should expand upon the number and type of agents to be considered. In so doing, new agents may be prioritized for research where a paucity of knowledge remains. One area of expansion would be increased inclusion of common food and water borne illness that represent constant burdens on the population.

Efforts were made to include emerging agents in this assessment. These agents, either altogether new to the human population (Hendra, Nipah) or prone to mutation (influenza) represent some of the most pressing concerns for natural outbreaks as seen by the H1N1 influenza strain currently circulating the globe. Those agents with a propensity to mutate may also be altered in man-made preparation of a bioterrorism agent for intentional distribution. Mutated agents will likely present challenges to successful medical intervention, affecting the realized public health impact. Although several of these agents were included in the assessment, defining a metric to quantify mutation potential remains unrealized. Forward thinking biopreparedness planners would greatly benefit from the ability to determine not only what significant threats exist under current condition, but also what may be the most pressing agents of concern tomorrow.

As previously stated, the methodology chosen for the present assessment reduced the inherent level of bias and uncertainty. However, these factors could not be completely eliminated due to the individual judgment required in the literature review and the selection of data points needed to inform the process. The next step would be independent verification of the data utilized in this report. The strength of this report, as well as future reports, would be improved after a third party review of the data inputs (outlined in Appendix B). While this process would serve to validate the present report, the same procedure could be used to review changes in available knowledge in the biopreparedness field. Changes noted during the review process could then be incorporated in routine updates vital for continued assessment of the chosen biopreparedness strategy.

Conclusion

Implementation of this methodology has addressed many of the critiques of past assessments and has attempted to further the state of the biopreparedness field. Results garnered through previous assessments have often disagreed due to different assumptions carried out through separate evaluations. The present analysis has been able to unify, to a great extent, the disparate results of the field to date. The use of all available data captured through a detailed literature review demonstrated the range of low to high impacts posed by each agent. A core public health impact formula was developed to illustrate and measure a pathway of infection to disease manifestation. The core formula was multiplied by possible consequences including severe morbidity and mortality levels both before and after treatment.

Through this analysis both well known and emerging agents were singled out for their ability to inflict public health burdens. When all agents were evaluated according to their level of untreated mortality, bacterial and viral agents both resulted in significant and roughly equal public health impacts. However, after the implementation of available medical countermeasures, viral agents dominated the top rankings indicating they would pose greater potential public health impacts. This result suggests that there is room for additional development of countermeasures targeted to high consequence viral agents. In a world of finite resources, findings of this nature are critical to policy makers looking for quantifiable opportunities to improve biopreparedness.

The described methodology has made advancements along many fronts. Despite this there is need for continued improvement in the biopreparedness disciple. Reaching consensus regarding the quality and completeness of variable attributes, reliability of included data and suitability of a single mathematical formula to describe expected impact are all worthy objectives for future research. As evident by the results of this report, the determination of those agents with the highest potential for public health impact was dependent on the analysis inputs. Only through the inclusion of the complete range of possibilities can any one assessment hope to address the complexity of the problem.

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Appendices

Appendix A: Public Health Impact Assessment Metric Reference

METRIC	DEFINITION	DATA ANALYSIS	SCALE
Geographic Range (endemic)	Number of continents in which the agent is either always present in the environment/ population or experienced in predictable patterns. An agent was considered endemic if so cited in the literature or if a continent reported a case/outbreak on an annual basis. The continents considered were: Africa, Asia, Australia, Europe, North America, and South America. Antarctica was excluded because it lacks a native population.	For each continent in which an agent was considered endemic, a value of 1 was assigned. 1 = 1 continent 2 = 2 continents, etc. If an agent was identified as endemic on all continents considered, a value of 6 was assigned. Possible: 0 - 6 Realized: 0 - 6 Impact is directly proportional to endemic geographic range value.	Normalized to achieve 0 - 1 scale. (Value-minimum value)/(maximum value-minimum value)
Availability	The number of years since the last reported case (human or animal). A reference date of August 27, 2007 was utilized for consistency.	A value of 1 was assigned to each year without a reported case. A year scale was chosen to minimize differences associated with seasonal frequency. 0 - 1 year = 1 1 - 2 years = 2 2 - 3 years = 3, etc. Possible: 1 - beginning of recorded history Realized: 1 - 30 years Impact is inversely proportional to the value of availability.	Normalized to achieve 0-1 scale. 1 - ((value-minimum value)/(maximum value-minimum value))

METRIC	DEFINITION	DATA ANALYSIS	SCALE
Growth Technology	The simplest means by which an agent can be reproduced.	A numerical value was assigned based on the difficulty level of the simplest growth technology cited in the literature. A higher value was assigned to the simplest, and therefore most easily replicated, method. 4 = broth 3 = small animal or egg inoculation 2 = cell culture 1 = large animal inoculation. Possible: 1 - 4 Realized: 1 - 4 Impact is directly proportional to growth technology.	Normalized to achieve 0-1 scale. (Value-minimum value)/(maximum value-minimum value)
Growth Concentration	The maximum concentration of plaque forming units (viral) or colony forming units (bacteria) per milliliter of an agent as identified in the available scientific literature.	Possible: 0 - infinite PFU/ml or CFU/ml Realized: 6.6×10^5 PFU/ml - 2×10^{10} PFU/ml Impact is directly proportional to growth concentration.	Normalized to achieve 0 - 1 scale. (Value-minimum value)/(maximum value-minimum value)
Infectious Dose 50 (ID_{50})	The number of organisms or virons required to infect fifty percent of the exposed population as reported in the available scientific literature.	Possible: 1 - infinite organisms/virons. Realized: 1 - 10^{11} organisms/virons. Impact is inversely proportional to ID_{50}.	Normalized to achieve 0 - 1 scale. 1 - ((value-minimum value)/(maximum value-minimum value))

METRIC	DEFINITION	DATA ANALYSIS	SCALE
Routes of Infection	Significant pathways for which the agent has been known to infect humans. Three possible routes of infection were considered: Inhalation- intake of aerosolized particles through the respiratory system. Ingestion- oral intake of infectious particles by themselves or in combination with food or water. Direct Contact- infection caused primarily through dermal contact with the infectious agent to include bite transmission via a vector (mosquito, tick, dog), introduction of infectious particles through abrasions in the skin, mucus membranes, or transfer (sexual or fomite) between individuals.	Entries were limited to 3 possible routes including inhalation, ingestion, and direct contact. A value of 1 was assigned for each significant routes of infection. 1 = 1 route 2 = 2 routes 3 = 3 routes Possible: 1 - 3 routes Realized: 1 - 3 routes Impact is directly proportional to the number of available pathways for infection.	Normalized to achieve 0 - 1 scale. (Value-minimum value)/(maximum value-minimum value)
Person-to-Person (P-P) Transmission	The ability of the agent to spread directly from person to person. P-P transmission is measured as the number of secondary cases caused by a single case where P-P transmission is the reported cause.	Possible: 0 - infinite cases Realized: 0 - 38 cases Impact is directly proportional P-P transmission.	Normalized to achieve 0 - 1 scale. (Value-minimum value)/(maximum value-minimum value)

METRIC	DEFINITION	DATA ANALYSIS	SCALE
Incubation Period	The number of days between infection and expression of illness.	Possible: 0 - infinite days Realized: 0.125 - 10,585 days Impact is inversely proportional to length of incubation period.	Normalized to achieve 0 - 1 scale. 1 - ((value-minimum value)/(maximum value-minimum value))
Stability	Stability is measured as one minus the percent of decay, where decay is defined as the percentage of the agent loss (biological or physical decay) per minute when exposed to the ambient environment.	Possible: 0 - 100% Realized: 0.0167 - 100% Impact is directly proportional to stability.	Normalization formula not applied.
Morbidity	A persistent state of ill health experienced as a result of disease caused by an agent. Morbidity is measured as the percentage of the population experiencing long term, severe effects lasting at least one year after the acute disease stage. Severe morbidity was assessed as a state of ill health affecting normal daily life to include: Neurologic disability, Inability to function independently, Blindness, Deafness, Amputation, etc.	Possible: 0 - 100% Realized: 0 - 70% Impact is directly proportional to the long term, severe morbidity.	Normalization formula not applied.

METRIC	DEFINITION	DATA ANALYSIS	SCALE
Mortality, Untreated	The percentage of the population who would die as a normal outcome of disease if treatment were either not provided or not available.	Possible: 0 - 100% Realized: 0 - 100% Impact is directly proportional to untreated mortality.	Normalization formula not applied.
Efficacy of Optimal Counter-measures	The effectiveness of all available pre and post-exposure treatment regiments. Efficacy is measured as the percentage of infected individuals who do not die due to available treatment options.	Possible: 0 - 100% Realized: 0 - 100% Impact is inversely proportional to bacterial and viral pre and post exposure efficacies.	Normalization formula not applied.
Mortality, Treated	The percentage of the population who would die as a normal outcome of disease acquired after agent infection despite application of available treatment options.	Possible: 0 - 100% Realized: 0 - 97% Impact is directly proportional to treated mortality.	Normalization formula not applied.

Appendix B: Public Health Impact Assessment Summary Data

BACTERIAL AGENTS (DISEASE)	AVAILABILITY (YEARS)	GEOGRAPHIC RANGE (ENDEMIC CONTINENTS)	GROWTH TECHNOLOGY (MEDIUM REQUIRED)	GROWTH CONCENTRATION (MAXIMUM CONCENTRATION)
Bacillus anthracis (Anthrax)	1[1]	3[2]	Broth[3]	1.5×10^9 CFU/ml[4]
Brucella species (Brucellosis)	1[5]	4[6]	Broth[7]	10^9 CFU/ml[8]
Burkholderia mallei (Glanders)	1[9]	3[10]	Broth[11]	10^{10} CFU/ml[12]
Burkholderia pseudomallei (Melioidosis)	1[13]	3[14]	Broth[15]	5×10^9 CFU/ml[16]
Chlamydia psittaci (Psittacosis)	1[17]	6[18]	Egg inoculation[19]	3.6×10^9 CFU/ml
Coxiella burnetii (Q fever)	1[20]	6[21]	Egg inoculation[22]	7.9×10^8 CFU/ml[23]
Francisella tularensis (Tularemia)	1[24]	3[25]	Broth[26]	10^8 CFU/ml[27]
Rickettsia prowazekii (Typhus fever)	1[28]	4[29]	Egg inoculation[30]	3.6×10^9 CFU/ml
Rickettsia rickettsii (Rocky Mountain spotted fever)	1[31]	2[32]	Egg inoculation[33]	10^7 CFU/ml[34]
Salmonella typhi (Typhoid fever)	1[35]	3[36]	Broth[37]	4×10^9 CFU/ml[38]
Salmonellosis (Salmonella)	1[39]	6[40]	Broth[41]	10^9 CFU/ml[42]
Shigella species (Shigella)	1[43]	6[44]	Broth[45]	10^6 CFU/ml[46]
Vibrio cholerae (Cholera)	1[47]	4[48]	Broth[49]	2×10^{10} CFU/ml[50]
Yersinia pestis (Plague)	1[51]	4[52]	Broth[53]	10^8 CFU/ml[54]

BACTERIAL AGENTS (DISEASE)	ROUTES OF INFECTION (NUMBER)	DECAY RANGE (%/MIN)	INFECTIOUS DOSE RANGE (ID_{50})	INCUBATION PERIOD RANGE (DAYS)
Bacillus anthracis (Anthrax)	3[55]	0.0167-5%[56] (0.1%)	2,000-55,000 organisms[57] (9,000)[58]	1-45[59] (5.5)
Brucella species (Brucellosis)	3[60]	2%[61] (2%)	10-100 organisms[62] (55)	1-168[63] (31.5)
Burkholderia mallei (Glanders)	2[64]	0.0167-10% (3.3%)	$1-10^{10}$ organisms (110,083)	3-14[65] (4)
Burkholderia pseudomallei (Melioidosis)	3[66]	3.4-6.8%[67] (4.5%)	$1-10^{10}$ organisms (110,083)	2-10,585[68] (11)
Chlamydia psittaci (Psittacosis)	3[69]	0.64-6.73%[70] (3.7%)	$1-10^{10}$ organisms (110,083)	1-47[71] (15.5)
Coxiella burnetii (Q fever)	3[72]	0.1-10%[73] (4%)	1-10 organisms[74] (4.5)	7-48[75] (17.5)
Francisella tularensis (Tularemia)	3[76]	0.7-8.7%[77] (4.7%)	5-1000 organisms[78] (27.5)	1-21[79] (4.5)
Rickettsia prowazekii (Typhus fever)	2[80]	0.0167-10% (3.3%)	10 organisms[81] (10)	6-15[82] (10.5)
Rickettsia rickettsii (Rocky Mountain spotted fever)	2[83]	0.0167-10% (3.3%)	10 organisms[84] (10)	2-14[85] (7)
Salmonella typhi (Typhoid fever)	1[86]	0.0167-10% (3.3%)	100,000 organisms[87] (100,000)	5-21[88] (13)
Salmonellosis (Salmonella)	1[89]	2-7.8%[90] (5.4%)	$50-10^{10}$ organisms[91] (10^5)	0.16-3[92] (1.58)
Shigella species (Shigella)	1[93]	0.0167-10% (3.3%)	$5-10^8$ organisms[94] (255)	1-7[95] (2)
Vibrio cholerae (Cholera)	1[96]	0.0167-10% (3.3%)	$1000-10^{11}$ organisms[97] (10^6)	0.125-5[98] (2.5)
Yersinia pestis (Plague)	2[99]	2%[100] (2%)	100-3,000 organisms[101] (1550)	1-6[102] (3)

BACTERIAL AGENTS (DISEASE)	P-P TRANS-MISSION (R_0)	MORBIDITY (%)	UN-TREATED MORTALITY (%)	OPTIMAL EFFICACY (%)	TREATED MORALITY (%)
Bacillus anthracis (Anthrax)	None	None	5-100%[103] (89%)	45-92.5%[104] (68.75%)	0-97%[105] (47.5%)
Brucella species (Brucellosis)	None	None	1-5%[106] (2%)	61-100%[107] (81%)	0%[108] (0%)
Burkholderia mallei (Glanders)	None	None	90-95%[109] (92.5%)	0% (0%)	20-50%[110] (35%)
Burkholderia pseudomallei (Melioidosis)	None	None	10-90%[111] (50%)	49-80%[112] (64.5%)	14-74%[113] (44%)
Chlamydia psittaci (Psittacosis)	None	None	15-33%[114] (24%)	100%[115] (100%)	0%[116] (0%)
Coxiella burnetii (Q fever)	None	None	0.5%-2%[117] (1.25%)	95-100%[118] (97.5%)	0%[119] (0%)
Francisella tularensis (Tularemia)	None	None	7-50%[120] (28.5%)	71.4-100%[121] (85.7%)	1.4-2%[122] (1.7%)
Rickettsia prowazekii (Typhus fever)	None	None	10-60%[123] (35%)	95-100%[124] (100)	0%[125] (0%)
Rickettsia rickettsii (Rocky Mountain spotted fever)	None	Long Term[126] 35% (35%)	15-30%[127] (22.5%)	96.5-99%[128] (97.8%)	1.1-5.3%[129] (3.2%)
Salmonella typhi (Typhoid fever)	None	None	5-30%[130] (17.5%)	0-99%[131] (96%)	0.3-50%[132] (0.7%)
Salmonellosis (Salmonella)	None	None	0.0017%[133] (0.0017%)	76.5%[134] (76.5%)	0.0004%[135] (0.0004%)
Shigella species (Shigella)	None	None	1.2-20%[136] (4%)	0-95.5%[137] (68.8%)	0.9-13%[138] (1.25%)
Vibrio cholerae (Cholera)	None	None	1-50%[139] (25%)	100%[140] (100%)	0%[141] (0%)
Yersinia pestis (Plague)	0-13[142] (1.3)	None	50-100%[143] (100%)	0-95%[144] (60%)	5%-50%[145] (40%)

VIRAL AGENTS (DISEASE)	AVAILABIL-ITY (YEARS)	GEOGRAPHIC RANGE (NUMBER OF ENDEMIC CONTINENT)	GROWTH TECHNOLOGY (MEDIUM REQUIRED)	GROWTH CONCENTRATION (MAXIMUM CONCENTRATION)
Alphavirus (Chikungunya fever)	1[146]	2[147]	Small animal[148]	1.9×10^8 PFU/ml
Alphavirus (Eastern equine encephalitis)	1[149]	2[150]	Egg inoculation[151]	1.9×10^8 PFU/ml
Alphavirus (Venezuelan equine encephalitis)	4[152]	0[153]	Egg inoculation[154]	1.9×10^8 PFU/ml
Alphavirus (Western equine encephalitis)	9[155]	0[156]	Cell culture[157]	1.9×10^8 PFU/ml
Arenavirus (Junin hemorrhagic fever)	7[158]	1[159]	Cell culture[160]	3.0×10^6 PFU/ml[161]
Arenavirus (Lassa fever)	1[162]	1[163]	Cell culture[164]	2.5×10^7 PFU/ml[165]
Arenavirus (Machupo)	1[166]	1[167]	Cell culture[168]	6.6×10^5 PFU/ml[169]
Filovirus (Ebola)	5[170]	0[171]	Small animal[172]	2.5×10^6 PFU/ml[173]
Filovirus (Marburg)	1[174]	0[175]	Small animal[176]	1.9×10^8 PFU/ml
Flavivirus (Dengue fever)	1[177]	4[178]	Cell culture[179]	10^7 PFU/ml[180]
Flavivirus (Japanese encephalitis)	1[181]	2[182]	Small animal[183]	10^9 PFU/ml[184]
Flavivirus (Yellow fever)	1[185]	2[186]	Large animal[187]	1.1×10^8 PFU/ml[188]
Flavivrus (Tick-borne encephalitis)	1[189]	2[190]	Cell culture[191]	1.9×10^8 PFU/ml
Influenza virus A (H5N1)	1[192]	0[193]	Egg inoculation[194]	1.9×10^8 PFU/ml
Paramyxoviridae (Hendra)	3[195]	0[196]	Cell culture[197]	1.9×10^8 PFU/ml
Paramyxoviridae (Nipah)	1[198]	1[199]	Cell culture[200]	2.0×10^8 PFU/ml[201]
Phlebovirus (Rift Valley fever)	1[202]	1[203]	Cell culture[204]	1.9×10^8 PFU/ml
Rhabdovirus (Rabies)	1[205]	6[206]	Small animal[207]	$10^{8.7}$ PFU/ml[208]
Variola major (Smallpox)	30[209]	0[210]	Cell culture[211]	5.0×10^7 PFU/ml[212]

VIRAL AGENTS (DISEASE)	ROUTES OF INFECTION (NUMBER OF ROUTES)	DECAY (%/MIN)	INFECTIOUS DOSE (ID$_{50}$)	INCUBATION PERIOD (DAYS)
Alphavirus (Chikungunya fever)	1[213]	0.56-100% (3.6%)	1-100 virons (25.3)	1-12[214] (4.5)
Alphavirus (Eastern equine encephalitis)	1[215]	0.56-100% (3.6%)	10-100 virons[216] (55)	3-15[217] (9)
*Alphavirus (*Venezuelan equine encephalitis)	2[218]	1.5-5.7%[219] (3.6%)	10-100 virons[220] (55)	1-6[221] (3.5)
*Alphavirus (*Western equine encephalitis)	1[222]	0.56-100% (3.6%)	10-100 virons[223] (55)	5-15[224] (10)
*Arenavirus (*Junin hemorrhagic fever)	3[225]	0.56-100% (3.6%)	1-100 virons (25.3)	7-21[226] (11.5)
*Arenavirus (*Lassa fever)	3[227]	1.3-6.9%[228] (4.1%)	1-10 virons[229] (5.5)	5-21[230] (13)
*Arenavirus (*Machupo)	3[231]	0.56-100% (3.6%)	1-10 virons[232] (5.5)	7-16[233] (11.5)
Filovirus (Ebola)	3[234]	0.56-100% (3.6%)	1-10 virons[235] (5.5)	1-21[236] (8.5)
Filovirus (Marburg)	3[237]	100%[238] (100%)	1-10 virons[239] (5.5)	2-14[240] (6.5)
Flavivirus (Dengue fever)	1[241]	0.56-100% (3.6%)	1-100 virons (25.3)	3-14[242] (5.5)
Flavivirus (Japanese encephalitis)	2[243]	2.6-4.0%[244] (3.3%)	1-100 virons (25.3)	5-15[245] (10)
Flavivirus (Yellow fever)	2[246]	1.48-7.04%[247] (4.26%)	1-10 virons[248] (5.5)	3-6[249] (4.5)
Flavivrus (Tick-borne encephalitis)	3[250]	0.56-100% (3.6%)	1-100 virons (25.3)	4-28[251] (10.5)
Influenza virus A (H5N1)	3[252]	0.56-100% (3.6%)	1-100 virons (25.3)	2-17[253] (5)
Paramyxoviridae (Hendra)	2[254]	0.56-100% (3.6%)	1-100 virons (25.3)	5-6[255] (5.5)
Paramyxoviridae (Nipah)	2[256]	0.56-100% (3.6%)	1-100 virons (25.3)	4-56[257] (13.5)
Phlebovirus (Rift Valley fever)	2[258]	0.9-10.1%[259] (5.5%)	1-10 virons[260] (5.5)	2-6[261] (4)
Rhabdovirus (Rabies)	3[262]	0.56-100% (3.6%)	1-100 virons (25.3)	7-2190[263] (57.5)
Variola major (Smallpox)	2[264]	0.56-0.86%[265] (0.71%)	3-100 virons[266] (55)	1-56[267] (12)

VIRAL AGENTS (DISEASE)	PERSON-TO-PERSON TRANS-MISSION (R_0)	MORBIDITY (%)	UN-TREATED MORTALITY (%)	TREAT-MENT EFFICACY (%)	TREATED MORALITY (%)
Alphavirus (Chikungunya fever)	None	None	0%[268] (0%)	None	0%[269]
Alphavirus (Eastern equine encephalitis)	None	Long Term[270] 35-50% (35%)	33-75%[271] (54%)	None	33-75%[272] (54%)
*Alphavirus (*Venezuelan equine encephalitis)	None	None	0-1%[273] (0.5%)	None	0-1%[274] (0.5%)
*Alphavirus (*Western equine encephalitis)	None	Long Term[275] 5-30% (17.5%)	3-15%[276] (3.5%)	None	3-15%[277] (3.5%)
*Arenavirus (*Junin hemorrhagic fever)	None	None	5-35%[278] (22.5%)	95-98%[279] (96.5%)	0-16.5%[280] (8.8%)
*Arenavirus (*Lassa fever)	None	Long Term[281] 10-33% (21.5%)	12-50%[282] (31%)	0-72% (41.9%)	14-22%[283] (18%)
Arenavirus (Machupo)	None	None	5-30%[284] (25%)	None	5-30%[285] (25%)
Filovirus (Ebola)	1.34-1.83[286] (1.63)	None	30-90%[287] (60%)	None	30-90%[288] (60%)
Filovirus (Marburg)	0-2[289] (1)	None	21-93%[290] (57%)	None	21-93%[291] (57%)
Flavivirus (Dengue fever)	None	None	12.5-50%[292] (31.25%)	0-100% (79.4%)	0-12.9%[293] (6.45%)
Flavivirus (Japanese encephalitis)	None	Long Term[294] 15-70% (42.5%)	20-60%[295] (30%)	91-98.5%[296] (94.75%)	3-50%[297] (7.5%)
Flavivirus (Yellow fever)	None	None	3-50%[298] (7.5%)	95-99%[299] (97%)	0-40%[300] (30%)
Flavivrus (Tick-borne encephalitis)	None	Long Term[301] 8.5-10% (10%)	0-40%[302] (30%)	95-99%[303] (97%)	0.75-2%[304] (1.375%)
Influenza virus A (H5N1)	0-6[305] (3)	None	33-80%[306] (56.5%)	0-58.8% (29.4%)	33-80%[307] (56.5%)
Paramyxoviridae (Hendra)	None	None	67%[308] (67%)	None	67%[309] (67%)
Paramyxoviridae (Nipah)	0-2[310] (1)	None	38.5-75%[311] (56.75%)	None	36.32-40%[312] (38.16%)
Phlebovirus (Rift Valley fever)	None	Long Term[313] 1-10% (5.5%)	0.5-50%[314] (0.75%)	0-99% (49.5%)	0.5-50%[315] (0.75%)
Rhabdovirus (Rabies)	None	Long Term[316] 60% (60%)	100%[317] (100%)	100%[318]	0%[319]
Variola major (Smallpox)	0-38[320] (1.4)	Long Term[321] 1% (1%)	10-95%[322] (30%)	0-96.8% (90%)	3-94%[323] (3%)

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