



INSTITUTE FOR DEFENSE ANALYSES

**2012 Review on the Extension of the
AMedP-8(C) Methodology to New Agents,
Materials, and Conditions**

Lucas A. LaViolet
Julia K. Burr
Carl A. Curling, Project Leader

October 2013

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Executive Summary

In 2005, the Institute for Defense Analyses (IDA) began developing a methodology for the North Atlantic Treaty Organization (NATO) to estimate casualties from chemical, biological, radiological, and nuclear (CBRN) weapons. The final draft documenting this methodology was published by IDA in 2009 and was promulgated by NATO in March 2011 as *Allied Medical Publication 8 (C): NATO Planning Guide for the Estimation of CBRN Casualties, (AMedP-8(C))*. Because *AMedP-8(C)* included a limited number of CBRN agents and effects, IDA has been asked each year since 2009 by the Army Office of the Surgeon General (OTSG) to review published literature to evaluate how the *AMedP-8(C)* methodology can be updated and expanded to new agents, materials, and conditions. This document, the 2012 review, fulfills both OTSG and NATO requirements and is the fourth in a series of annual reviews, updated as the scope of *AMedP-8(C)* expands. This annual review focuses primarily on newly available data that can be used to update existing agents or effects in the methodology.

This review is structured into four chapters. The introductory chapter states the objective of the 2012 annual review as well as the task requirements it fulfills. It also briefly introduces the *AMedP-8(C)* casualty estimation methodology and summarizes the past annual reviews and subsequent programs of work completed by IDA. Chapter 2, “The 2012 Review,” describes the literature review process and reports the major findings by agent. When new data could be used to update or extend the *AMedP-8(C)* methodology, the level of effort to incorporate these data or perform follow-on analyses was estimated in Chapter 3. Finally, Chapter 4 recommends topics for future analysis identified in this and prior reviews.

The key findings of the literature review, summarized by agent in Chapter 2, focus on human cases of exposure, advancements in medical countermeasure development, and response data from animal models. These summaries serve two purposes: 1) to identify data sources immediately useful to updating *AMedP-8(C)* human response parameters or otherwise modifying the methodology and 2) to help inform future analyses and to serve as a starting point for related research efforts.

The literature review revealed three different categories of work that could be carried out to update or extend the *AMedP-8(C)* methodology: editorial changes to the text of future versions of *AMedP-8* or related documents, the incorporation of new data into existing *AMedP-8(C)* models, and the comparison of *AMedP-8(C)* models to other published models for validation or revision. Estimates for the level of effort required to complete future analyses identified in this review were based on IDA’s prior experiences performing analyses in this field.

Based on IDA's understanding of the available literature and the needs of the sponsor, the IDA research team recommends a number of future efforts related to *AMedP-8(C)* human response modeling.

1. As a NATO document, *AMedP-8(C)* is subject to a periodic review every three years. Since its 2011 publication, the *AMedP-8(C)* methodology has been expanded to include human response parameters for additional agents and the consideration of medical care. Given these significant advancements, IDA recommends that a new version of *AMedP-8* be proposed at the 2014 review. The proposal should include incorporating, at a minimum, the new agents, the impact of medical care, and any editorial changes to keep the content current as described in this document.
2. During this review, the IDA team was successful in identifying new sources of data relevant to updating the *AMedP-8(C)* methodology. In particular, data are available that could impact the anthrax, botulism, brucellosis, glanders, plague, Q fever, smallpox, and tularemia models. In addition, IDA continues to pursue access to the human response studies conducted through the military research volunteer (MRV) program in the 1950s and 1960s, which could provide data useful to the Q fever, SEB, and tularemia models. IDA should conduct cost-benefit analyses to determine whether the new data would significantly improve the military medical planning process and warrant changes to the *AMedP-8(C)* methodology.
3. The IDA team should quantify the impact on the casualty estimate of radioprotectant drugs, radiation mitigators, and radiation therapeutic agents in NATO member national inventories or those in procurement, but not fielded. As many of these countermeasures are Food and Drug Administration-approved or have emergency use investigational new drug (IND) status, some efficacy data must be available.
4. Case histories from the SEARCH (System for Evaluation and Archiving of Radiation accidents based on Case Histories) radiation effects database should be reviewed to assess their value in validating or revising the *AMedP-8(C)* radiological agent human response models. In addition to requesting access to the SEARCH database, IDA should reach out to and collaborate with the Group to Link nonhuman Primate and Human radiation effects (GLiPH), which is leveraging the SEARCH data to establish correlations between human and non-human primate radiation exposures. With a better understanding of the GLiPH team's efforts, IDA can determine how their work might fit within the framework of the *AMedP-8(C)* methodology.
5. The IDA team should compare the *AMedP-8(C)* dose-response models to the alternative dose-response models discovered in this literature review and any other published models. In particular, alternative dose-response models specific to anthrax and radiation were discovered, as well as a more general method of pooling infectivity data from multiple species. Analyses should be conducted to compare each alternative

methodology with the existing models within *AMedP-8(C)*. The result of these analyses should be a recommendation to continue with the current methodology or to change it, along with an estimate of the level of effort required to do so.

6. Many chemical and biological agents of interest to various government agencies are candidates for future inclusion in *AMedP-8(C)*. Levels of effort to incorporate more than 40 agents into the *AMedP-8(C)* methodology were estimated in the 2009 review, yet only a small fraction has since been modeled. IDA should develop a prioritization scheme for future inclusion of the remaining agents in *AMedP-8(C)* based on an analysis of the military threat or capability to NATO nations and the availability of modeling data for each agent.
7. As discussed in prior annual reviews, IDA stands ready to investigate the feasibility of incorporating the estimation of psychological casualties into the *AMedP-8(C)* methodology if and when this becomes a sponsor priority.

Contents

1.	Introduction	1
	A. Objective	1
	B. Task Requirements	1
	C. Background	2
	D. Past Reviews and Subsequent Program of Work	3
2.	The 2012 Review	5
	A. Approach	5
	B. Biological Agents	6
	1. Anthrax	6
	2. Botulism	15
	3. Brucellosis	17
	4. Glanders	19
	5. Plague	20
	6. Q Fever	24
	7. Staphylococcal Enterotoxin B (SEB)	26
	8. Smallpox	27
	9. Tularemia	31
	10. Venezuelan Equine Encephalitis (VEE)	34
	C. Chemical Agents	36
	1. Distilled Mustard (HD)	36
	2. Sarin (GB) and Methylphosphonothioic Acid (VX)	38
	D. Radiation	40
	1. Human Cases	40
	2. Medical Countermeasures	41
	3. Animal Models	43
3.	Estimation of Effort Required to Extend <i>AMedP-8</i> Methodology	45
	A. Introduction	45
	B. Editorial Changes	45
	C. Incorporation of New Data into Existing Models	45
	D. Evaluation of Alternative Models	46
4.	Recommended Future Analyses	49
	Appendix A. References	A-1
	Appendix B. Abbreviations	B-1

1. Introduction

A. Objective

In 2005, the Institute for Defense Analyses (IDA) began developing a methodology for the North Atlantic Treaty Organization (NATO) to estimate casualties from chemical, biological, radiological, and nuclear (CBRN) weapons. The final draft documenting this methodology was published by IDA in 2009 and was promulgated by NATO in March 2011 as *Allied Medical Publication 8 (C): NATO Planning Guide for the Estimation of CBRN Casualties, (AMedP-8(C))*. Because *AMedP-8(C)* included a limited number of CBRN agents and effects, IDA has been asked each year since 2009 by the Army Office of the Surgeon General (OTSG) to review published literature to evaluate how the *AMedP-8(C)* methodology can be updated and expanded to new agents, materials, and conditions. This 2012 annual review focuses primarily on newly available data that can be used to update existing agents or effects in the methodology. IDA's literature review included new and updated data sources for currently modeled CBRN agents and effects, novel medical countermeasures, and alternative human response models.

This review is in four chapters. This introductory chapter states the objective of the 2012 annual review as well as the requirements it fulfills. It also briefly introduces the *AMedP-8(C)* casualty estimation methodology and summarizes past annual reviews and subsequent programs of work completed by IDA. Chapter 2, "The 2012 Review," describes the literature review process and reports the major findings by agent. When new data could be used to update or extend the *AMedP-8(C)* methodology, the level of effort to incorporate these data or perform follow-on analyses was estimated in Chapter 3. Finally, Chapter 4 recommends topics for future analysis identified in this and prior reviews.

B. Task Requirements

This document describes analysis completed under Task Order CA-6-3079 "CBRN Casualty Estimation Update of the Medical CBRN Defense Planning and Response Project," Subtask 2 "Update Agents/Materials into *AMedP-8(C)* Methodology." The task order specifies a "draft program of work identifying agents, effects, materials, and conditions of interest to the DOD [Department of Defense] (and NATO and other Federal agencies, as requested), but not currently included in *AMedP-8(C)*." This document is not an addendum to *AMedP-8(C)*, but may be considered a supplement to the *AMedP-8(C) Technical Reference Manual*.¹

¹ Carl A. Curling et al., *Technical Reference Manual: Allied Medical Publication 8(C), NATO Planning Guide for the Estimation of Chemical, Biological, Radiological, and Nuclear (CBRN) Casualties*, IDA Document D-4082 (Alexandria, VA: IDA, August 2010).

C. Background

AMedP-8(C) describes a general methodology that military planners use to estimate casualties from CBRN weapons. The annexes to *AMedP-8(C)* define specific modeling parameters for three chemical agents (sarin (GB), methylphosphonothioic acid (VX), and distilled mustard (HD)), five biological agents (those that cause anthrax, botulism, pneumonic plague, smallpox, and Venezuelan equine encephalitis (VEE)), seven radioisotopes (^{60}Co , ^{90}Sr , ^{131}I , ^{137}Cs , ^{192}Ir , ^{238}Pu , and ^{241}Am), and acute nuclear blast, radiation, and thermal effects.

The *AMedP-8(C)* methodology depends on a national transport and dispersal model to specify the amount of CBRN agent or effect where individuals in the scenario are located. The methodology then characterizes human response to exposure as a stepwise function of injury severity over time (called an injury profile). Based on the available toxicity data for chemical, radiological, and nuclear agents and effects, clinically distinguishable dose/dosage/insult ranges are developed for each agent or effect, and injury profiles are drawn for all ranges. Individuals are considered casualties at the time the injury profile first reaches a user-defined injury severity level.

For biological agents, the following five submodels are combined to determine the number of casualties over time.

1. The infectivity submodel estimates the number of individuals that become ill as a function of inhaled dose of agent.
2. The incubation period submodel estimates the time from exposure to the onset of symptoms.
3. The duration of illness submodel estimates the time from onset of symptoms to either death or recovery.
4. The disease profile submodel divides the illness into clinically differentiable stages and assigns each an injury severity level.
5. The lethality submodel estimates the number of individuals that die.

Just like for the chemical, radiological, and nuclear methodologies, individuals are considered casualties when the symptoms from a biological agent exposure (as defined by the disease profile submodel) reach a user-defined threshold.

With the exceptions of prophylaxis for anthrax, plague, and smallpox, *AMedP-8(C)* does not consider the effects of medical countermeasures on the casualty estimate. This was due to a restriction imposed by NATO that medical intervention be excluded from the methodology because it was not standardized across all NATO nations.

D. Past Reviews and Subsequent Program of Work

In 2009, the same year IDA published the final draft of *AMedP-8(C)*, it was asked to nominate new agents to be considered for future versions of *AMedP-8*. The resulting analysis identified nearly 900 chemical and biological materials of concern to various governmental agencies. A representative subset of agents was further reviewed for availability of human response modeling data. Based on literature reviews, IDA estimated the level of effort required to extend the *AMedP-8(C)* methodology to include these new agents. This analysis, along with estimates of the level of effort to include psychological or civilian casualties, made up the *2009 Report on the Extension of the AMedP-8(C) Methodology to New Agents, Materials, and Conditions*.² This became the first in a series of annual reviews to update and expand the *AMedP-8(C)* methodology.

In the following year, IDA published the ratification draft of *AMedP-8(C)*,³ as well as its technical reference manual,⁴ which documented the derivation of the underlying parameters. In addition, human response parameters were developed for five additional biological agents: staphylococcal enterotoxin B (SEB), and the causative agents of brucellosis, glanders, Q fever, and tularemia.⁵ The second annual review⁶ recommended extending the *AMedP-8(C)* methodology to include the impact of medical care and adding new agents to *AMedP-8(C)* to better align it with the Common User Database (CUD), a U.S. tool that estimates the medical requirements for different types of patients. Since the outputs of the *AMedP-8(C)* methodology are roughly equivalent to the inputs to the CUD, including the same CBRN agents and effects in both methodologies would benefit planners.

The 2011 program of work included modeling medical intervention for all CBRN agents and effects in *AMedP-8(C)* as well as for the five additional biological agents modeled in 2010.⁷

² Carl A. Curling, Lucas A. LaViolet, and Julia K. Burr, *2009 Report on the Extension of the AMedP-8(C) Methodology to New Agents, Materials, and Conditions* (Alexandria, VA: Institute for Defense Analyses (IDA), October 2009).

³ North Atlantic Treaty Organization (NATO), *AMedP-8(C): NATO Planning Guide for the Estimation of Chemical, Biological, Radiological, and Nuclear (CBRN) Casualties*, STANAG 2553 (Brussels: NATO, March 2011).

⁴ Curling et al., *Technical Reference Manual: AMedP-8(C)*.

⁵ Carl A. Curling et al., *Parameters for the Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia*, IDA Document D-4132 (Alexandria, VA: IDA, November 2010); Carl A. Curling et al., *Addenda to Allied Medical Publication 8, "NATO Planning Guide for the Estimation of Chemical, Biological, Radiological, and Nuclear (CBRN) Casualties" (AMedP-8(C))—Parameters for Estimation of Casualties from Exposure to Specified Biological Agents*, IDA Document D-4133 (Alexandria, VA: IDA, January 2011).

⁶ Carl A. Curling, Lucas A. LaViolet, and Julia K. Burr, *2010 Review on the Extension of the AMedP-8(C) Methodology to New Agents, Materials, and Conditions*, IDA Document D-4131 (Alexandria, VA: IDA, December 2010).

⁷ Carl A. Curling et al., *The Impact of Medical Care on Casualty Estimates from Battlefield Exposure to Chemical, Biological and Radiological Agents and Nuclear Weapon Effects*, IDA Document D-4465 (Alexandria, VA: IDA, March 2012); Carl A. Curling et al., *Addenda to Allied Medical Publication 8, "NATO*

The third annual review⁸ prioritized an analysis of the effect of bioscavengers on chemical nerve agents, the inclusion of historical data from experiments with military research volunteers (MRV) from the U.S. offensive weapons program, and the expansion of the methodology to include a number of additional agents of interest to the sponsor.

In 2012, IDA began developing human response modeling parameters for five new chemical agents (chlorine, cyanogen chloride, hydrogen cyanide, hydrogen sulfide, and phosgene) and seven new biological agents (ricin, T-2 mycotoxin, and the causative agents of eastern equine encephalitis, Ebola, Marburg, melioidosis, and western equine encephalitis). In addition, IDA investigated the potential use of bioscavengers to treat chemical injuries and sought access to the set of MRV exposure data for Q fever, SEB, and tularemia.

Planning Guide for the Estimation of Chemical, Biological, Radiological, and Nuclear (CBRN) Casualties" (AMedP-8(C)) to Consider the Impact of Medical Treatment on Casualty Estimation, IDA Document D-4466 (Alexandria, VA: IDA, December 2012).

⁸ Carl A. Curling, Lucas A. LaViolet, and Julia K. Burr, *2011 Review on the Extension of the AMedP-8(C) Methodology to New Agents, Materials, and Conditions*, IDA Document D-4486 (Alexandria, VA: IDA, December 2011).

2. The 2012 Review

A. Approach

The 2012 review focused on identifying potential new data sources for the CBRN agents and effects in *AMedP-8(C)* and the subsequently published addenda on the five new biological agents and medical care. Explicitly excluded from the review was information related to the five chemical agents and seven biological agents still under development. IDA reviewed publicly available, peer-reviewed literature from 2009 to the present to identify relevant references published since the original development of the *AMedP-8(C)* human response parameters.

The primary collection of articles was gathered using EBSCOHost.⁹ For the initial literature search, the agent name for chemical agents and disease name for biological agents were used. Because the goal was to collect and review summary references that might serve as a starting point for future analyses, rather than identifying every potential change to *AMedP-8(C)*, the search results were filtered to reduce the number of articles to review. For example, there were more than 16,000 results for the term *anthrax* searched in “all text.” When narrowing the search terms to *anthrax* in “subject terms” and *review* in “abstract” and also filtering by language (English) and reference type (academic journals), the results were reduced to 76. In addition to the EBSCOHost searches, PubMed¹⁰ searches were performed specifically for recently published reports of animal (ideally non-human primate) models to characterize the pathology of disease or develop a median infective or lethal dose estimate.

To supplement the peer-reviewed journal articles with more recent outbreak information from around the world, reports were gathered from the Program for Monitoring Emerging Diseases (ProMED) website.¹¹ In addition, articles and mortality tables of notifiable diseases from the Centers for Disease Control and Prevention’s (CDC) *Morbidity and Mortality Weekly Report (MMWR)* were useful in identifying recent cases in the United States. The U.S. Food and Drug Administration (FDA) website¹² and ClinicalTrials.gov¹³ were also valuable resources for determining the status of novel medical countermeasures in development.

⁹ See the EBSCOHost website at <http://www.ebscohost.com/>.

¹⁰ The PubMed search tool is hosted by the National Center for Biotechnology Information website at <http://www.ncbi.nlm.nih.gov/pubmed/>.

¹¹ ProMED is “an Internet-based reporting system dedicated to rapid global dissemination of information on outbreaks of infectious diseases and acute exposures to toxins that affect human health, including those in animals and in plants grown for food or animal feed.” For more information, visit the ProMED website at <http://www.promedmail.org/>.

¹² See the U.S. Food and Drug Administration (FDA) website at <http://www.fda.gov/>.

The major findings of the literature review are summarized by agent in the following sections. Subjects of focus include human cases of exposure, advancements in medical countermeasure development, and response data from animal models. These summaries serve two purposes: 1) identifying data sources immediately useful to updating *AMedP-8(C)* human response parameters or otherwise modifying the methodology and 2) helping to inform future analyses and serve as a starting point for related research efforts.

Topics related to the first purpose are highlighted in Chapters 3 and 4, where future analyses are recommended and the level of effort is estimated for each. On the other hand, data not currently applicable to the *AMedP-8(C)* methodology, such as medical countermeasure test data for items not in national military inventories, are still worth capturing both to help anticipate which countermeasures may be fielded in the future, and to facilitate and expedite data collection and analysis if and when countermeasures are fielded. As another example, endemic disease data may be secondary to data from more controlled studies for deriving human response parameters, but descriptions of human disease can still benefit modeling, and variations in human disease rates may indicate changes in the agent or host that may become militarily relevant.

B. Biological Agents

1. Anthrax

a. Human Cases

Since the appearance of anthrax-contaminated letters in October 2001, much of the attention on anthrax in the United States has focused on its use as a weapon of bioterrorism and the threat of an aerosolized attack. The current literature review highlighted the fact that anthrax is still endemic to many parts of the world, and natural human illness is almost always associated with direct or indirect contact with infected animals. More than 40 countries reported suspected or confirmed human anthrax cases since 2009, with no evidence of malicious intent in any case.¹⁴ Of note were large-scale outbreaks of human anthrax that affected Bangladesh in recent years, with hundreds of people contracting cutaneous or gastrointestinal anthrax after butchering and consuming the meat of contaminated animals.¹⁵

¹³ Clinicaltrials.gov, a service of the U.S. National Institutes of Health, is “a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world.” See <http://clinicaltrials.gov/> for more information.

¹⁴ See the search results for posts with the keyword *anthrax since 2009* at <http://www.promedmail.org/>.

¹⁵ Apurba Chakraborty et al., “Anthrax Outbreaks in Bangladesh, 2009–2010,” *American Journal of Tropical Medicine and Hygiene* 86, no. 4 (2012): 703–710; Muhammad Afsar Siddiqui et al., “Recent Outbreak of Cutaneous Anthrax in Bangladesh: Clinico-Demographic Profile and Treatment Outcome of Cases Attended at Rajshahi Medical College Hospital,” *BMC Research Notes* 5 (2012): 464.

1) Injection Anthrax

In addition to the Bangladesh cases and a number of other cutaneous outbreaks in recent years, the literature review revealed several more unusual incidents with anthrax. For instance, recent anthrax outbreaks in Europe among heroin users infected through the injection of anthrax-contaminated drugs led to the definition of a new type of anthrax dubbed injection anthrax.¹⁶ This form of anthrax is associated with severe pain and swelling at the injection site, but the black eschars associated with cutaneous anthrax were notably absent.¹⁷ In an outbreak in 2009–2010, there were 47 laboratory-confirmed and an additional 72 suspected cases of injection anthrax in Scotland. Of the 119 Scottish cases, there were 14 reported deaths.¹⁸ There were also five confirmed anthrax cases in England and three in Germany.¹⁹ A second outbreak began in June 2012 and infected at least 15 heroin-injecting drug-users in Germany (1 death, 3 survivors), Denmark (1 death, 1 survivor), France (1 survivor), Scotland (1 death, 1 survivor), Wales (1 survivor), and England (4 deaths, 1 survivor) through March 2013.²⁰ A comprehensive summary of the first outbreak in Scotland, including data on the clinical presentation of cases, was prepared by the Health Protection Scotland.²¹

¹⁶ R. Grunow et al., “Anthrax among Heroin Users in Europe Possibly Caused by Same *Bacillus anthracis* Strain since 2000,” *Euro Surveillance* 18, no. 13 (2013): 1–9; Erin P. Price et al., “Molecular Epidemiologic Investigation of an Anthrax Outbreak among Heroin Users, Europe,” *Emerging Infectious Diseases* 18, no. 8 (2012): 1307–1313; T. Holzmann et al., “Fatal Anthrax Infection in a Heroin User from Southern Germany, June 2012,” *Euro Surveillance* 17, no. 26 (2012): 2–6; Caitlin W. Hicks et al., “An Overview of Anthrax Infection Including the Recently Identified Form of Disease in Injection Drug Users,” *Intensive Care Medicine* 38, no. 7 (2012): 1092–1104; Daniel A. Sweeney et al., “Anthrax Infection,” *American Journal of Respiratory and Critical Care Medicine* 184, no. 12 (2011): 1333–1341; Arfon G. M. T. Powell et al., “A Case of Septicaemic Anthrax in an Intravenous Drug User,” *BMC Infectious Diseases* 11 (2011): 21; National Anthrax Outbreak Control Team, *An Outbreak of Anthrax among Drug Users in Scotland, December 2009 to December 2010* (Glasgow, Scotland: Health Protection Scotland, December 2011).

¹⁷ Hicks et al., “Overview of Anthrax Infection.”

¹⁸ Grunow et al., “Anthrax among Heroin Users”; Price et al., “Investigation of an Anthrax Outbreak”; C. N. Ramsay et al., “An Outbreak of Infection with *Bacillus anthracis* in Injecting Drug Users in Scotland,” *Euro Surveillance* 15, no. 2 (2010); National Anthrax Outbreak Control Team, *Anthrax among Drug Users in Scotland*.

¹⁹ Grunow et al., “Anthrax among Heroin Users.”

²⁰ Ibid.; ProMED-mail, “Anthrax—Germany: (BY) Fatal, Heroin User” (International Society for Infectious Diseases (ISID), 2012); ProMED-mail, “Anthrax—Germany (02): (BY) 2nd Heroin Case, RFI” (ISID, 2012); ProMED-mail, “Anthrax—Germany (06): (Berlin) New Case” (ISID, 2012); ProMED-mail, “Anthrax, Human—Denmark (03): Fatal Conf. Heroin Case” (ISID, 2012); ProMED-mail, “Anthrax—France: (RA) Conf. Heroin Case” (ISID, 2012); ProMED-mail, “Anthrax, Human—UK (02): (Scotland) New Heroin Related Case, Alert” (ISID, 2012); ProMED-mail, “Anthrax, Human—Denmark (04): 2nd Heroin Associated Case” (ISID, 2012); ProMED-mail, “Anthrax, Human—UK (05): (England) New Heroin Case” (ISID, 2012); ProMED-mail, “Anthrax, Human—UK (06): (Wales) New Heroin Case” (ISID, 2012); ProMED-mail, “Anthrax, Human—UK (07): (England) Fatal” (ISID, 2012); ProMED-mail, “Anthrax—Germany (09): (Berlin) New Case in Addict” (ISID, 2012); ProMED-mail, “Anthrax, Human—UK (11): (England) New Heroin Case” (ISID, 2012); ProMED-mail, “Anthrax, Human—UK (12): (England) New Heroin Case, Fatal” (ISID, 2012); ProMED-mail, “Anthrax—UK: (England) New Fatal Heroin Case” (ISID, 2013); ProMED-mail, “Anthrax—UK (02): (Scotland) New Fatal Heroin Case” (ISID, 2013).

²¹ National Anthrax Outbreak Control Team, *Anthrax among Drug Users in Scotland*.

2) U.S. Human Cases

Only two anthrax cases have been reported in the United States since 2009.²² The first was the 2009 gastrointestinal anthrax infection of a 24-year-old woman from a presumed aerosol exposure at an event using animal-hide drums in New Hampshire.²³ The exact route of entry in this case is unclear, although it is suspected that the “spores were either relatively large or clumped and were aerosolized and then swallowed.”²⁴ Alternatively, it is possible that the woman consumed food or water that was contaminated by aerosolized spores.²⁵ Once the diagnosis of gastrointestinal anthrax was made, the patient was treated with intravenous (IV) anthrax immune globulin in addition to antibiotics and was only the fifth person in the world to receive this treatment.²⁶ After nearly two months in the hospital, the patient was transferred to a rehabilitation facility and was discharged 20 days later.²⁷

The second American case was the 2011 inhalation anthrax infection in a Florida man on vacation in Montana, Wyoming, and the Dakotas.²⁸ On 4 August, near the end of his trip, he became ill and was admitted to a hospital in Minnesota, where he was diagnosed with inhalational anthrax before being transferred to another hospital on 7 August. Like the New Hampshire woman, this patient was treated with anthrax immune globulin from the CDC (reportedly the 19th person to receive this treatment), which may have helped his recovery. Fluid was also drained from the patient’s lungs, which was reported to be essential to survival in a prior case of inhalational anthrax.²⁹ On 29 August the patient was released from the hospital after more than three weeks of treatment. The source of exposure remains unknown, although it is suspected that he was exposed to spores in the soil during his vacation.

²² Centers for Disease Control and Prevention (CDC), “Notifiable Diseases and Mortality Tables,” *Morbidity and Mortality Weekly Report (MMWR)* 62, no. 32 (2013): 438–451.

²³ L. Mayo et al., “Gastrointestinal Anthrax after an Animal-Hide Drumming Event: New Hampshire and Massachusetts, 2009,” *MMWR* 59, no. 28 (2010): 872–877; Mark S. Klempner et al., “Case 25-2010: A 24-Year-Old Woman with Abdominal Pain and Shock,” *New England Journal of Medicine* 363, no. 8 (2010): 766–777.

²⁴ Klempner et al., “Case 25-2010.”

²⁵ Mayo et al., “Gastrointestinal Anthrax.”

²⁶ Klempner et al., “Case 25-2010.”

²⁷ Mayo et al., “Gastrointestinal Anthrax”; Klempner et al., “Case 25-2010.”

²⁸ Robert Roos, “Early Diagnosis, Treatment Helped Florida Man Beat Anthrax,” *Center for Infectious Disease Research and Policy (CIDRAP) News* (30 August 2011), <http://www.cidrap.umn.edu/cidrap/content/bt/anthrax/news/aug3011anthrax.html>.

²⁹ James J. Walsh et al., “A Case of Naturally Acquired Inhalation Anthrax: Clinical Care and Analyses of Anti-Protective Antigen Immunoglobulin G and Lethal Factor,” *Clinical Infectious Diseases* 44, no. 7 (2007): 968–971.

b. Medical Countermeasures

1) Anthrax Vaccines

In May 2012 the FDA approved an abbreviated primary dosing schedule for the currently licensed anthrax vaccine, BioThrax (formerly known as Anthrax Vaccine Adsorbed). The primary dosing schedule was changed from a five-shot series (at 0, 1, 6, 12, and 18 months) plus annual boosters to a three-shot series (at 0, 1, and 6 months) plus boosters at 12 and 18 months followed by annual boosters thereafter.³⁰ This change reflects the evidence that protective antibody levels are achieved after the first three doses of BioThrax, although frequent boosters are still required to maintain protective levels.³¹

Additional studies with BioThrax are also underway to test other uses for the vaccine. Participants are currently being recruited for a five-year clinical trial to determine any adverse effects of BioThrax administered to pregnant women³² and a Phase II study to determine the effect of a three dose series of BioThrax on the effectiveness of ciprofloxacin.³³ A Phase III trial to demonstrate the effectiveness of a three-dose series of BioThrax as post-exposure prophylaxis has also been completed.³⁴ In the meantime, although BioThrax is not FDA-approved for post-exposure prophylaxis, it has been used in a three-dose regimen along with the regular 60-day course of antibiotics under an investigational new drug (IND) protocol.³⁵

Anthrax vaccine research in children may also be forthcoming. In March 2013, the Presidential Commission for the Study of Bioethical Issues released its recommendations for pre- and post-event medical countermeasure research on anthrax vaccination in children.³⁶ It outlined the circumstances in which it might be permissible to perform anthrax vaccination research in children and specified a preferred age de-escalation procedure that might infer that research on the next oldest age group poses minimal risk.

³⁰ Wellington Sun, “May 17, 2012 Approval Letter—BioThrax,” last modified 21 May 2012, <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm304758.htm>.

³¹ Alexandra Worobec, “Summary Basis for Regulatory Action,” U.S. Food and Drug Administration (FDA), 17 May 2012, <http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM308410.pdf>.

³² “BioThrax (Anthrax Vaccine Adsorbed) Vaccine in Pregnancy Registry,” ClinicalTrials.gov, last modified 23 July 2013, <http://clinicaltrials.gov/show/NCT01653392>.

³³ “Ciprofloxacin BioThrax Co-Administration Study,” ClinicalTrials.gov, last modified 23 July 2013, <http://clinicaltrials.gov/show/NCT01753115>.

³⁴ “Immunogenicity and Safety Study of a Three-Dose BioThrax® Regimen for Post-Exposure Prophylaxis in Healthy Adults,” ClinicalTrials.gov, last modified 19 June 2012, <http://clinicaltrials.gov/show/NCT01491607>.

³⁵ Anette Schneemann and Marianne Manchester, “Anti-Toxin Antibodies in Prophylaxis and Treatment of Inhalation Anthrax,” *Future Microbiology* 4, no. 1 (2009): 35–43; Carmen Maher, “FDA Anthrax Preparedness,” in *Improving a Path Forward: New Steps in Anthrax Planning Public Health Preparedness Summit* (Anaheim, CA: FDA, 2012).

³⁶ Presidential Commission for the Study of Bioethical Issues, *Safeguarding Children: Pediatric Medical Countermeasure Research* (Washington, DC: U.S. Department of Health & Human Services, March 2013).

Despite the proven efficacy of BioThrax, anthrax vaccine research is an ongoing and high priority effort, and a number of recent reports have summarized the latest developments.³⁷ Briefly, anthrax lethality is attributed to two virulence factors: (1) the toxin comprised of three proteins (protective antigen (PA), lethal factor (LF), and edema factor (EF)) and (2) the capsule.³⁸ Although live spore-based vaccines have been effective in preventing disease in animals and are still used in humans by some nations, such as those from the former Soviet Union, other nations favor acellular rather than whole-spore vaccines for fear of residual virulence.³⁹ Both the UK Anthrax Vaccine Precipitated and the U.S. BioThrax are sterile, acellular vaccines with PA as the main protective component.⁴⁰

As a result of ongoing efforts to develop a second generation recombinant protective antigen (rPA)-based anthrax vaccine, a number of candidate rPA vaccines have already completed Phase I clinical trials to test for safety in humans. Among the rPA anthrax vaccine candidates advancing to or already undergoing Phase II (effectiveness) clinical trials are SparVax, an *E. coli*-based rPA vaccine created by PharmAthene;⁴¹ GC1109, a vaccine developed by the Green Cross Corporation;⁴² and PreviThrax, a product of Emergent BioSolutions (the producer of the licensed BioThrax vaccine).⁴³ Emergent BioSolutions is also recruiting participants for a Phase II trial of another “next-generation” vaccine candidate, NuThrax, also

³⁷ Arthur M. Friedlander and Stephen F. Little, “Advances in the Development of Next-Generation Anthrax Vaccines,” *Vaccine* 27 Suppl 4 (2009): D28–32; Robert J. Cybulski, Jr., Patrick Sanz, and Alison D. O'Brien, “Anthrax Vaccination Strategies,” *Molecular Aspects of Medicine* 30, no. 6 (2009): 490–502; Theodor Chitlaru et al., “Progress and Novel Strategies in Vaccine Development and Treatment of Anthrax,” *Immunological Reviews* 239 (2011): 221–236; J. M. Beierlein and A. C. Anderson, “New Developments in Vaccines, Inhibitors of Anthrax Toxins, and Antibiotic Therapeutics for *Bacillus anthracis*,” *Current Medicinal Chemistry* 18, no. 33 (2011): 5083–5094.

³⁸ Zhaochun Chen, Mahtab Moayeri, and Robert Purcell, “Monoclonal Antibody Therapies against Anthrax,” *Toxins* 3, no. 8 (2011): 1004–1019; Jon Oscherwitz, Fen Yu, and Kemp B. Cease, “A Synthetic Peptide Vaccine Directed against the 2β2–2β3 Loop of Domain 2 of Protective Antigen Protects Rabbits from Inhalation Anthrax,” *Journal of Immunology* 185, no. 6 (2010): 3661–3668.

³⁹ Beierlein and Anderson, “New Developments in Vaccines.”

⁴⁰ Friedlander and Little, “Next-Generation Anthrax Vaccines,” Cybulski, Sanz, and O'Brien, “Anthrax Vaccination Strategies.”

⁴¹ “Phase II Study of Range and Schedule of rPA Doses,” ClinicalTrials.gov, last modified 12 September 2008, <http://www.clinicaltrials.gov/ct2/show/NCT00170456>; “Safety, Tolerability and Immunogenicity of Recombinant Anthrax Vaccine Adsorbed,” ClinicalTrials.gov, last modified 12 September 2008, <http://clinicaltrials.gov/ct2/show/NCT00170469>; “Anthrax Vax to Move into New Phase II Trials: Trial Planned for the Second Half of 2012,” Suzanne Elvidge, last modified 21 June 2012, <http://www.fiercevaccines.com/story/anthrax-vax-move-new-phase-ii-trials/2012-06-21>; “SparVax® rPA Anthrax Vaccine,” PharmAthene, Inc., accessed 29 July 2013, <http://www.pharmathene.com/product-portfolio/sparvax-rpa-anthrax-vaccine>.

⁴² “A Study to Assess Dose-Response, Efficacy (Immunogenicity) and the Safety of GC1109,” ClinicalTrials.gov, last modified 27 June 2013, <http://clinicaltrials.gov/show/NCT01624532>; “Pipeline,” Green Cross, accessed 29 July 2013, <http://www.greencross.com/eng/research/pipelineall.do>.

⁴³ “Emergent Pipeline,” Emergent BioSolutions, accessed 21 August 2013, <http://emergentbiosolutions.com/?q=node/42>.

known as AV7909, which is made of BioThrax combined with a novel immunostimulatory compound, CPG 7909.⁴⁴

A variety of other vaccine approaches are also being explored including plant-based⁴⁵ and synthetic peptide vaccines⁴⁶ directed at specific domains of the PA protein and a technique encapsulating rPA with a particulate carrier.⁴⁷ Other vaccine candidates are being developed that aim to improve the protection of a PA-based vaccine by targeting other components of the bacteria as well. Multi-component subunit vaccines have been developed that target PA in combination with spore antigens,⁴⁸ LF,⁴⁹ and poly-gamma-D-glutamic acid (PGA) capsule components.⁵⁰ There are also efforts to develop vaccines comprised of killed but metabolically active (KBMA) whole bacterial cells.⁵¹

The development of vaccines that protect against multiple pathogens represents another potential way forward. Based on pre-clinical studies, a dual vaccine candidate that inoculates against smallpox and anthrax “not only is superior in immunogenicity and efficacy in comparison with the currently licensed vaccines against smallpox and anthrax, but also remedies the inadequacies associated with such licensed vaccines.”⁵²

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- ⁴⁴ “A Phase 2 Safety and Immunogenicity Study for an Anthrax Vaccine Using 3 Schedules and Two Dose Levels,” ClinicalTrials.gov, last modified 16 September 2013, <http://clinicaltrials.gov/show/NCT01770743>; Robert J. Hopkins et al., “Randomized, Double-Blind, Placebo-Controlled, Safety and Immunogenicity Study of 4 Formulations of Anthrax Vaccine Adsorbed Plus CPG 7909 (AV7909) in Healthy Adult Volunteers,” *Vaccine* 31, no. 30 (2013): 3051–3058; “Emergent Pipeline.”
- ⁴⁵ Jyotsna Gorantala et al., “A Plant Based Protective Antigen [PA(dIV)] Vaccine Expressed in Chloroplasts Demonstrates Protective Immunity in Mice against Anthrax,” *Vaccine* 29, no. 27 (2011): 4521–4533.
- ⁴⁶ Oscherwitz, Yu, and Cease, “Synthetic Peptide Vaccine.”
- ⁴⁷ Kevin L. Schully et al., “Rapid Vaccination Using an Acetalated Dextran Microparticulate Subunit Vaccine Confers Protection against Triplicate Challenge by *Bacillus anthracis*,” *Pharmaceutical Research* 30, no. 5 (2013): 1349–1361.
- ⁴⁸ Trupti N. Brahmhatt et al., “Recombinant Exosporium Protein BclA of *Bacillus anthracis* Is Effective as a Booster for Mice Primed with Suboptimal Amounts of Protective Antigen,” *Infection and Immunity* 75, no. 11 (2007): 5240–5247; C. K. Cote et al., “Characterization of a Multi-Component Anthrax Vaccine Designed to Target the Initial Stages of Infection as Well as Toxaemia,” *Journal of Medical Microbiology* 61, no. Pt 10 (2012): 1380–1392.
- ⁴⁹ Les W. Baillie et al., “An Anthrax Subunit Vaccine Candidate Based on Protective Regions of *Bacillus anthracis* Protective Antigen and Lethal Factor,” *Vaccine* 28, no. 41 (2010): 6740–6748.
- ⁵⁰ Deog-Yong Lee et al., “Poly-Gamma-D-Glutamic Acid and Protective Antigen Conjugate Vaccines Induce Functional Antibodies against the Protective Antigen and Capsule of *Bacillus anthracis* in Guinea-Pigs and Rabbits,” *FEMS Immunology and Medical Microbiology* 57, no. 2 (2009): 165–172.
- ⁵¹ Justin Skoble et al., “Killed but Metabolically Active *Bacillus anthracis* Vaccines Induce Broad and Protective Immunity against Anthrax,” *Infection and Immunity* 77, no. 4 (2009): 1649–1663.
- ⁵² Tod J. Merkel et al., “Development of a Highly Efficacious Vaccinia-Based Dual Vaccine against Smallpox and Anthrax, Two Important Bioterror Entities,” *Proceedings of the National Academy of Sciences of the United States of America* 107, no. 42 (2010): 18091–18096.

2) Anti-Toxin Therapies

Post-exposure therapy with monoclonal antibodies has been another area of recent research with scientists developing antibodies against all three proteins (PA, LF, and EF) and the capsule,⁵³ a number of which are being studied in human clinical trials.⁵⁴ Raxibacumab (ABThrax), a human monoclonal antibody against rPA, has acquired FDA approval for use as a supplement to antibiotic therapy and is in the U.S. Strategic National Stockpile (SNS).⁵⁵

Another antibody therapeutic that is stored in the SNS is anthrax immune globulin (AIG), which is a polyclonal antibody derived from the pooled plasma of individuals vaccinated with BioThrax.⁵⁶ AIG is considered an IND by the CDC, but has been used in combination with approved antibiotics to treat patients in the European injection anthrax cases,⁵⁷ the 2011 Minnesota inhalation anthrax case,⁵⁸ and the 2009 gastrointestinal case in New Hampshire.⁵⁹

c. Animal Models

For much of the last century, rhesus macaques were the primary non-human primate used in experiments with anthrax.⁶⁰ In addition to the studies already identified in the technical reference manual for *AMedP-8(C)*, a 2001 study to determine the inhalation anthrax LD₅₀ in rhesus

⁵³ Jeffrey W. Froude, 2nd, Philippe Thullier, and Thibaut Pelat, “Antibodies against Anthrax: Mechanisms of Action and Clinical Applications,” *Toxins* 3, no. 11 (2011): 1433–1452; Zhaochun Chen, Mahtab Moayeri, and Robert Purcell, “Monoclonal Antibody Therapies against Anthrax,” *Toxins* 3, no. 8: 1004–1019; Ulrich vor dem Esche et al., “Passive Vaccination with a Human Monoclonal Antibody: Generation of Antibodies and Studies for Efficacy in *Bacillus anthracis* Infections,” *Immunobiology* 216, no. 7 (2011): 847–853; Parul Kulshreshtha and Rakesh Bhatnagar, “Inhibition of Anthrax Toxins with a Bispecific Monoclonal Antibody That Cross Reacts with Edema Factor as Well as Lethal Factor of *Bacillus anthracis*,” *Molecular Immunology* 48, no. 15–16 (2011): 1958–1965; Hicks et al., “Overview of Anthrax Infection.”

⁵⁴ “Safety and Pharmacokinetics Study of Human Monoclonal Antibody (AVP-21D9),” ClinicalTrials.gov, last modified 20 November 2012, <http://clinicaltrials.gov/show/NCT01202695>; “Dose Escalation Study of Valortim® (MDX-1303) Administered Intravenously (IV) in Healthy, Normal Subjects,” ClinicalTrials.gov, last modified 6 June 2011, <http://clinicaltrials.gov/ct2/show/NCT01265745>; “Anthrax-rPA: Safety, Tolerability, Immunogenicity,” ClinicalTrials.gov, last modified 26 August 2010, <http://clinicaltrials.gov/show/NCT00063843>.

⁵⁵ “FDA Approves Raxibacumab to Treat Inhalational Anthrax,” FDA, last modified 18 December 2012, <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm332341.htm>; Sohini Mazumdar, “Raxibacumab,” *mAbs* 1, no. 6 (2009): 531–538; “GSK Receives FDA Approval for Raxibacumab Anti-Toxin for the Treatment of Inhalational Anthrax,” GlaxoSmithKline, last modified 14 December 2012, <http://www.gsk.com/media/press-releases/2012/gsk-receives-fda-approval-for-raxibacumab-anti-toxin-for-the-tre.html>; Andrew W. Artenstein and Steven M. Opal, “Novel Approaches to the Treatment of Systemic Anthrax,” *Clinical Infectious Diseases* 54, no. 8 (2012): 1148–1161.

⁵⁶ Schneemann and Manchester, “Anti-Toxin Antibodies.”

⁵⁷ Ramsay et al., “Outbreak of Infection with *Bacillus anthracis*.”

⁵⁸ Roos, “Early Diagnosis, Treatment Helped Florida Man Beat Anthrax.”

⁵⁹ Klempner et al., “Case 25-2010.”

⁶⁰ N. A. Twenhafel, “Pathology of Inhalational Anthrax Animal Models,” *Veterinary Pathology* 47, no. 5 (2010): 819–830.

macaques was recently ascertained.⁶¹ It identified four strains of *B. anthracis* and calculated LD₅₀ values for each, which ranged from 6,700 to 40,100,000 spores. A 1995 document by Fritz et al., which characterizes the pathology of inhalation anthrax in rhesus macaques, may also contain information on the infectivity and lethality.⁶²

Recently, the FDA Animal Rule has spurred investigations into other non-human primate models of inhalation anthrax for FDA approval of therapeutics in humans.⁶³ Publications based on this research revealed sources of additional data for use in calculating a median infective/lethal dose for the *AMedP-8(C)* inhalation anthrax model.

The cynomolgus macaque model was most recently characterized in a 2012 study by Henning et al.,⁶⁴ which built off the prior work of Vasconcelos et al.⁶⁵ The Vasconcelos study exposed 14 monkeys to aerosolized *B. anthracis* and determined an LD₅₀ of 61,800 spores and a probit slope of 4.21. However, it is unclear how these values were calculated since all 14 monkeys died. Moreover, the dose data for the individual monkeys were not published other than specifying a range of 45,600 to 2,940,000 spores. The Henning group reported the inhaled doses for each of the 12 cynomolgus macaques exposed in their experiment (in terms of the LD₅₀ calculated by Vasconcelos et al.). All monkeys were exposed to hundreds of times the calculated LD₅₀, yet two of them survived the challenge.

Other recent studies describe the pathology of inhalation anthrax in the African green monkey. One reports that the LD₅₀ for this species was previously determined to be 11,000 spores, although the data are unpublished.⁶⁶ This same study challenged nine monkeys to doses ranging from 210,000 to 18,900,000 spores, and all succumbed except one monkey at the lowest dose. In a similar experiment, 12 monkeys with inhaled doses ranging from 200 to 10,000,000

⁶¹ Roy Barnewall, James Estep, and Robert M. DeBell, *Inhalation Median Lethal Dose (LD₅₀) Determinations in Rhesus Monkeys Exposed to Bacillus anthracis* (Columbus, OH: Battelle Memorial Institute Medical Research and Evaluation Facility, 2001); Roy Barnewall, *Median Lethal Concentration (LC₅₀) Determinations in Rhesus Monkeys Challenged with Different Strains of Bacillus anthracis Spores* (Columbus, OH: Battelle Memorial Institute Medical Research and Evaluation Facility, 2000); Claire Matthews, *Anthrax LD₅₀ in Monkeys (Inhalation Exposure)* (Columbus, OH: Battelle Memorial Institute, 2001).

⁶² D. L. Fritz et al., "Pathology of Experimental Inhalation Anthrax in the Rhesus Monkey," *Laboratory Investigation* 73, no. 5 (1995): 691–702.

⁶³ Twenhafel, "Inhalational Anthrax Animal Models"; Lisa N. Henning et al., "Development of an Inhalational *Bacillus anthracis* Exposure Therapeutic Model in Cynomolgus Macaques," *Clinical and Vaccine Immunology* 19, no. 11 (2012): 1765–1775.

⁶⁴ Henning et al., "Inhalational *Bacillus anthracis* Exposure Therapeutic Model."

⁶⁵ Daphne Vasconcelos et al., "Pathology of Inhalation Anthrax in Cynomolgus Monkeys (*Macaca fascicularis*)," *Laboratory Investigation* 83, no. 8 (2003): 1201–1209.

⁶⁶ Cynthia A. Rossi et al., "Identification of a Surrogate Marker for Infection in the African Green Monkey Model of Inhalation Anthrax," *Infection and Immunity* 76, no. 12 (2008): 5790–5801.

spores all died, even though half were exposed to less than 10,000 spores.⁶⁷ Combining both studies, the estimated inhaled doses are known for 21 African green monkeys.

In 2013, Savransky et al. published an alternative to the well-established non-human primate models, characterizing a guinea pig model of inhalation anthrax.⁶⁸ The LD₅₀ was estimated to be 50,100 spores.

The control animals from various anthrax vaccine studies with rhesus macaques could also provide additional data points that could potentially be included in the calculation of infectivity or lethality parameters. In a 1993 study, one of ten monkeys survived challenge, but only the mean and standard deviation are given for the inhaled doses (400,000 ± 160,000 spores).⁶⁹ Similarly, the control animals in a number of other studies were reported to have died following lethal exposures, which are expressed as summary statistics rather than individual doses.⁷⁰ In contrast, the two controls for one study both died after exposures to specified amounts of agent (511 and 535 LD₅₀, where LD₅₀ = 5.5x10⁴ spores).⁷¹ In a study published in 1963, 28 rhesus macaques were exposed to aerosolized *B. anthracis*, and all but two died.⁷² The estimated doses for the two surviving monkeys were 10,100 and 10,400 spores, but the doses for the other monkeys were given in ranges.

d. Human Response Models

In a 2011 article,⁷³ Day et al. describe an alternative method for calculating the probability of death due to infection with anthrax. It is based on a two-compartment mathematical model and is dose-dependent and considers the timing of antibiotic intervention. This model is substantially

⁶⁷ N. A. Twenhafel, E. Leffel, and M. L. Pitt, "Pathology of Inhalational Anthrax Infection in the African Green Monkey," *Veterinary Pathology* 44, no. 5 (2007): 716–721.

⁶⁸ Vladimir Savransky et al., "Pathology and Pathophysiology of Inhalational Anthrax in a Guinea Pig Model," *Infection and Immunity* 81, no. 4 (2013): 1152–1163.

⁶⁹ Arthur M. Friedlander et al., "Postexposure Prophylaxis against Experimental Inhalation Anthrax," *Journal of Infectious Diseases* 167, no. 5 (1993): 1239–1242.

⁷⁰ M. L. M. Pitt et al., "Comparison of the Efficacy of Purified Protective Antigen and MDPH to Protect Non-Human Primates from Inhalation Anthrax," *Salisbury Medical Bulletin* S87 (1996): 130; B. E. Ivins et al., "Comparative Efficacy of Experimental Anthrax Vaccine Candidates against Inhalation Anthrax in Rhesus Macaques," *Vaccine* 16, no. 11–12 (1998): 1141–1148; P.F. Fellows et al., "Efficacy of a Human Anthrax Vaccine in Guinea Pigs, Rabbits, and Rhesus Macaques against Challenge by *Bacillus anthracis* Isolates of Diverse Geographical Origin," *Vaccine* 19, no. 23–24 (2001): 3241–3247.

⁷¹ B. E. Ivins et al., "Efficacy of a Standard Human Anthrax Vaccine against *Bacillus anthracis* Aerosol Spore Challenge in Rhesus Monkeys," *Salisbury Medical Bulletin* S87 (1996): 125–126.

⁷² C. A. Gleiser et al., "Pathology of Experimental Respiratory Anthrax in *Macaca mulatta*," *British Journal of Experimental Pathology* 44, no. 4 (1963): 416–426.

⁷³ Judy Day, Avner Friedman, and Larry S. Schlesinger, "Modeling the Host Response to Inhalation Anthrax," *Journal of Theoretical Biology* 276, no. 1 (2011): 199–208; Judy Day, Avner Friedman, and Larry S. Schlesinger, "Supplementary Materials for Modeling the Host Response to Inhalation Anthrax," *Journal of Theoretical Biology* 276, no. 1 (2011).

different from the current infection and lethality models in *AMedP-8(C)* in that it results in a nonzero fraction of the population becoming ill and surviving without treatment. Like the *AMedP-8(C)* treatment model, the Day model allows for treatment at various times. The duration of illness is not an explicit output of the model, although the authors state that it could be used to provide an approximate estimate of the time to death. It may be worth comparing the results of this model with the existing *AMedP-8(C)* model, which is dose-independent.

Egan et al.'s 2010 article identified a similar within-host model for calculating the probability of infection given an inhaled dose of anthrax and considers the effects of antibiotic prophylaxis.⁷⁴ Again, it may be worthwhile to compare the results of this model with those of the *AMedP-8(C)* infectivity model. The Egan article also reports levels of adherence with taking antibiotics, which may be useful to include in a treatment model for anthrax rather than assuming complete adherence to a prolonged antibiotic regimen. Another article also provides anthrax antibiotic adherence data collected via a survey of citizens across the country and specific areas affected by the 2001 anthrax attacks.⁷⁵

2. Botulism

a. Human Cases

From 2009 through 2012, more than 550 U.S. cases of botulism were reported to the CDC, categorized as infant (70%), foodborne (12%), or wound/unspecified (18%) botulism.⁷⁶ Among the wound botulism cases were a number who contracted the disease via contaminated heroin, similar to the injection anthrax cases in Europe. Historically, this has been a problem in California,⁷⁷ but recently there have also been cases reported in the states of Texas⁷⁸ and Washington.⁷⁹ No cases of inhalational botulism were identified in this literature review.

b. Medical Countermeasures

There is only one FDA-approved countermeasure for botulism in adults: BAT, a heptavalent antitoxin effective in neutralizing all seven known botulinum toxin serotypes (A, B,

⁷⁴ Joseph R. Egan et al., "Re-Assessment of Mitigation Strategies for Deliberate Releases of Anthrax Using a Real-Time Outbreak Characterization Tool," *Epidemics* 2, no. 4 (2010): 189–194.

⁷⁵ Gillian SteelFisher et al., "Public Response to an Anthrax Attack: Reactions to Mass Prophylaxis in a Scenario Involving Inhalation Anthrax from an Unidentified Source," *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science* 9, no. 3 (2011): 239–250.

⁷⁶ "Notifiable Diseases and Mortality Tables."

⁷⁷ Christopher Gouveia, Somnath Mookherjee, and Matthew S. Russell, "Wound Botulism Presenting as a Deep Neck Space Infection," *Laryngoscope* 122, no. 12 (2012): 2688–2689; Jean Yuan et al., "Recurrent Wound Botulism among Injection Drug Users in California," *Clinical Infectious Diseases* 52, no. 7 (2011): 862–866.

⁷⁸ ProMED-mail, "Botulism, Wound, Drug-Related—USA: (TX)" (ISID, 2011).

⁷⁹ ProMED-mail, "Botulism, Wound, Drug-Related—USA: (WA)" (ISID, 2010); ProMED-mail, "Botulism, Wound, Drug-Related—USA (02): (WA)" (ISID, 2011).

C, D, E, F, and G).⁸⁰ BAT, which is stockpiled in the SNS,⁸¹ replaced the licensed bivalent (A/B) antitoxin and the investigational serotype E antitoxin in March 2010.⁸² Still, the development of a vaccine to prevent botulism is ongoing, with multiple recombinant botulinum vaccine A/B candidates undergoing Phase II trials.⁸³ Another product, a drug known as Firdapse (3,4-diaminopyridine), has also undergone Phase II and III clinical trials to treat patients with botulism in a hospital in France.⁸⁴

c. Animal Models

In 2010 the findings of a study to determine the LD₅₀ and LCt₅₀ for inhaled botulinum toxin (serotypes A and B) in rhesus macaques was published as part of the process of establishing an appropriate animal model for inhalational botulism in compliance with the FDA Animal Rule for validating therapeutics for use in humans.⁸⁵ In all, 40 monkeys were exposed (18 to serotype A and 22 to serotype B) and the median lethal values were established via probit analysis. The actual inhaled doses could not be estimated for 4 of the 18 monkeys exposed to serotype A (the specific threat modeled in *AMedP-8(C)*), so the dose-response data include only 14 data points

⁸⁰ “Biodefense Products,” Cangene, accessed 30 July 2013, <http://www.cangene.com/biodefense-products>; “FDA Approves First Botulism Antitoxin for Use in Neutralizing All Seven Known Botulinum Nerve Toxin Serotypes,” FDA, last modified 22 March 2013, <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm345128.htm>; Jay S. Epstein, “March 22, 2013 Approval Letter—BAT,” FDA, last modified 21 June 2013, <http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm345137.htm>; “Alphabetical List of Licensed Products: Information Updated through August 31, 2013,” FDA, last modified 31 August 2013, <http://www.fda.gov/downloads/BiologicsBloodVaccines/UCM149970.pdf>.

⁸¹ “FDA Approves First Botulism Antitoxin”; Philip K. Russell and Gigi Kwik Gronvall, “U.S. Medical Countermeasure Development since 2001: A Long Way yet to Go,” *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science* 10, no. 1 (2012): 66–76.

⁸² CDC, “Investigational Heptavalent Botulinum Antitoxin (HBAT) to Replace Licensed Botulinum Antitoxin AB and Investigational Botulinum Antitoxin E,” *MMWR* 59, no. 10 (2010): 299; Mary Kate Hart et al., “Advanced Development of the rF1V and rBV A/B Vaccines: Progress and Challenges,” *Advances in Preventive Medicine* 2012 (2012).

⁸³ “Phase 3, Randomized, Safety, Lot Consistency and Clinical Benefit Study of Recombinant Botulinum Vaccine A/B (rBV A/B),” ClinicalTrials.gov, last modified 9 September 2013, <http://clinicaltrials.gov/show/NCT01940315>; “Safety, Tolerability, and Immunogenicity Study of Investigational Recombinant Botulinum Vaccine A/B (rBV A/B) in Volunteers Previously Immunized with Investigational Pentavalent Botulinum Toxoid,” ClinicalTrials.gov, last modified 5 February 2013, <http://clinicaltrials.gov/show/NCT01701999>; Hart et al., “rF1V and rBV A/B Vaccines.”

⁸⁴ “Pilot Study on the Usefulness of 3,4-Diaminopyridine in the Treatment of Botulism,” ClinicalTrials.gov, last modified 22 June 2012, <http://clinicaltrials.gov/show/NCT01441557>; Joseph S. Zakhari et al., “Formulating a New Basis for the Treatment against Botulinum Neurotoxin Intoxication: 3,4-Diaminopyridine Prodrug Design and Characterization,” *Bioorganic & Medicinal Chemistry* 19, no. 21 (2011): 6203–6209.

⁸⁵ Daniel C. Sanford et al., “Inhalational Botulism in Rhesus Macaques Exposed to Botulinum Neurotoxin Complex Serotypes A1 and B1,” *Clinical and Vaccine Immunology* 17, no. 9 (2010): 1293–1304; Daniel C. Sanford et al., “Inhalational Botulism in Rhesus Macaques Exposed to Botulinum Neurotoxin Complex Serotypes A1 and B1 (Supplement),” *Clinical and Vaccine Immunology* 17, no. 9 (2010): 1293–1304.

(which are tabulated in the online supplement to the study). From these data, the authors reported an LD₅₀ of 550 MIPLD₅₀/kg for serotype A, which is higher than the 350 MIPLD₅₀/kg estimate currently used in *AMedP-8(C)*.⁸⁶ [MIPLD is the mouse intraperitoneal lethal dose.] The study also defines the conversion of MIPLD₅₀ to grams as 3.2x10¹⁰ MIPLD₅₀/g (compared to 3.0x10¹⁰ MIPLD₅₀/g currently used as the conversion in *AMedP-8(C)*). If these values were used directly in *AMedP-8(C)* under the same assumption of a 70 kg man, the LD₅₀ would change from 0.8 µg/man to 1.2 µg/man. The report also lists the range of times to death for the eight animals (of the 18) that died, although the specific times for each animal are not provided. On the contrary, for the 22 monkeys exposed to serotype B, additional information (e.g., time to death for each animal) is captured in a second study published in 2011.⁸⁷

3. Brucellosis

a. Human Cases

Brucellosis, which is still endemic in large parts of the world, poses a significant public health risk, with an estimated 500,000 cases globally each year.⁸⁸ According to a 2012 report, annual incident rates were estimated to be as high as 268 per 100,000 persons in some regions of the world.⁸⁹ In the United States, brucellosis is relatively rare, with the annual number of cases averaging slightly more than 100 since 2009.⁹⁰ By way of comparison, China reported approximately 26,000 annual cases of human brucellosis from 2005–2010.⁹¹

b. Medical Countermeasures

Despite the global prevalence of brucellosis, there is still no vaccine licensed for use in humans.⁹² Live, attenuated vaccines have been used in the past on humans in the former Soviet

⁸⁶ Curling et al., *Technical Reference Manual: AMedP-8(C)*.

⁸⁷ Bryan A. Parks et al., “Quantification of Botulinum Neurotoxin Serotypes A and B from Serum Using Mass Spectrometry,” *Analytical Chemistry* 83, no. 23 (2011): 9047–9053.

⁸⁸ Zhijun Zhong et al., “Human Brucellosis in the People's Republic of China During 2005–2010,” *International Journal of Infectious Diseases* 17, no. 5 (2013): e289–292; Katie M. Eales, Robert E. Norton, and Natkunam Ketheesan, “Brucellosis in Northern Australia,” *American Journal of Tropical Medicine and Hygiene* 83, no. 4 (2010): 876–878; Thomas A. Ficht et al., “Brucellosis: The Case for Live, Attenuated Vaccines,” *Vaccine* 27 Suppl 4 (2009): D40–43; Vidya L. Atluri et al., “Interactions of the Human Pathogenic *Brucella* Species with Their Hosts,” *Annual Review of Microbiology* 65 (2011): 523–541; Mohamed N. Seleem, Stephen M. Boyle, and Nammalwar Sriranganathan, “Brucellosis: A Re-Emerging Zoonosis,” *Veterinary Microbiology* 140, no. 3–4 (2010): 392–398.

⁸⁹ Anna S. Dean et al., “Global Burden of Human Brucellosis: A Systematic Review of Disease Frequency,” *PLoS Neglected Tropical Diseases* 6, no. 10 (2012): e1865.

⁹⁰ “Notifiable Diseases and Mortality Tables.”

⁹¹ Zhong et al., “Brucellosis in the People's Republic of China.”

⁹² Stuart D. Perkins, Sophie J. Smither, and Helen S. Atkins, “Towards a *Brucella* Vaccine for Humans,” *FEMS Microbiology Reviews* 34, no. 3 (2010): 379–394; Seleem, Boyle, and Sriranganathan, “Brucellosis: A Re-Emerging Zoonosis.”

Union and in China, but their questionable efficacy and adverse side effects have precluded their use in other parts of the world.⁹³ The current treatment of brucellosis in humans is a regimen of two or more antibiotics, although a number of studies have shown that the choice of antibiotics (among those commonly used) does not have a significant impact on the effectiveness of treatment.⁹⁴ In past cases of brucellosis complicated by endocarditis, surgery in addition to antibiotic medical care corresponded to improved outcome.⁹⁵

c. Animal Models

As part of the process for acquiring FDA-approval for investigational vaccine candidates or other therapeutics under the Animal Rule, a research group has recently studied and validated both the mouse and rhesus macaque as appropriate models for testing therapeutics for inhalational brucellosis in humans.⁹⁶ In the non-human primate study, 16 rhesus macaques were exposed to aerosolized *B. melitensis* ranging from 5,440 to 511,000 CFU.⁹⁷ All became infected (as measured by bacteria in at least one tissue at the time of euthanasia), and at least 15 of the 16 were febrile at some point during the course of illness. The pathology of brucellosis in rhesus macaques was well characterized, and the study supports the suitability of this animal as a model to test therapeutics under the Animal Rule.

A 2011 article described how to combine dose-response data from multiple species using published brucellosis experimental data.⁹⁸ Not only were the experimental hosts different (mice, monkeys, and humans), but the routes of exposure differed as well. Using this method of pooling data from different studies, a beta-Poisson dose-response model was developed with an alpha value of 0.214149 and an N_{50} (median infective dose) of 1,885 CFU. This technique may be useful for not only brucellosis, but also other agent models in the *AMedP-8(C)* methodology. As this approach of combining dose-response data from multiple species and routes of exposure is in contrast to the hierarchy of data sources described in *AMedP-8(C)*, a comparison of the two approaches is worthwhile. If the data pooling method is found to be more suitable for estimating

⁹³ Perkins, Smither, and Atkins, “Towards a *Brucella* Vaccine for Humans”; Ficht et al., “Live, Attenuated Vaccines”; Zhong et al., “Brucellosis in the People’s Republic of China.”

⁹⁴ Maryam Keshtkar-Jahromi et al., “Medical Versus Medical and Surgical Treatment for *Brucella* Endocarditis,” *Annals of Thoracic Surgery* 94, no. 6 (2012): 2141–2146; R. Yousefi-Nooraie et al., “Antibiotics for Treating Human Brucellosis (Review),” *Cochrane Database of Systematic Reviews* 10 (2012); Seyed Mohammad Alavi and Mohammad Esmail Motlagh, “A Review of Epidemiology, Diagnosis and Management of Brucellosis for General Physicians Working in the Iranian Health Network,” *Jundishapur Journal of Microbiology* 5, no. 2 (2012): 384–387.

⁹⁵ Keshtkar-Jahromi et al., “Treatment for *Brucella* Endocarditis.”

⁹⁶ Lisa N. Henning et al., “Pathophysiology of the Rhesus Macaque Model for Inhalational Brucellosis,” *Infection and Immunity* 80, no. 1 (2012): 298–310; Lisa N. Henning et al., “The Pathophysiology of Inhalational Brucellosis in BALB/c Mice,” *Scientific Reports* 2 (2012): 495.

⁹⁷ Henning et al., “Rhesus Macaque Model for Inhalational Brucellosis.”

⁹⁸ Sondra S. Teske et al., “Animal and Human Dose-Response Models for *Brucella* Species,” *Risk Analysis* 31, no. 10 (2011): 1576–1596.

human response than choosing data from a single representative species and route of exposure, then most of the parameters in the *AMedP-8(C)* human response models would need to be revisited for possible inclusion of additional data sources.

4. Glanders

a. Human Cases

Glanders in humans is rare, and the literature review of documents published since 2009 resulted in no cases of human glanders. Much of the current research on glanders and its causative agent, *Burkholderia mallei*, is motivated by the pursuit of medical countermeasures. There is currently no licensed vaccine for preventing glanders in humans,⁹⁹ and antibiotic therapy is the only treatment available.¹⁰⁰

b. Medical Countermeasures

A vaccine for glanders is still very early in the development cycle, and multiple approaches are being investigated, including live attenuated vaccines, subunit vaccines, and killed bacteria vaccines.¹⁰¹ Major challenges remain, including validating appropriate animal models for future FDA approval and ensuring additional protection against melioidosis, a similar disease caused by a related *Burkholderia* species.¹⁰²

Little is known about the efficacy of antibiotic treatment of glanders, but *B. mallei* is known to be resistant to many antimicrobials.¹⁰³ Nevertheless, there are a number of antibiotics to which the bacterium is susceptible,¹⁰⁴ and prolonged therapy with a combination of these drugs is recommended.¹⁰⁵ Experimental therapy with monoclonal antibodies against *Burkholderia*

⁹⁹ Mitali Sarkar-Tyson et al., “Protective Efficacy of Heat-Inactivated *B. thailandensis*, *B. mallei* or *B. pseudomallei* against Experimental Melioidosis and Glanders,” *Vaccine* 27, no. 33 (2009): 4447–4451; D. Mark Estes et al., “Present and Future Therapeutic Strategies for Melioidosis and Glanders,” *Expert Review of Anti-Infective Therapy* 8, no. 3 (2010): 325–338; Daniel N. Wolfe, William Florence, and Paula Bryant, “Current Biodefense Vaccine Programs and Challenges,” *Human Vaccines & Immunotherapeutics* 9, no. 7 (2013); Leang-Chung Choh et al., “*Burkholderia* Vaccines: Are We Moving Forward?” *Frontiers in Cellular and Infection Microbiology* 3 (2013): 5; Ediane B. Silva and Steven W. Dow, “Development of *Burkholderia mallei* and *pseudomallei* Vaccines,” *Frontiers in Cellular and Infection Microbiology* 3 (2013): 10.

¹⁰⁰ Silva and Dow, “*Burkholderia mallei* and *pseudomallei* Vaccines.”

¹⁰¹ Ibid.

¹⁰² Wolfe, Florence, and Bryant, “Biodefense Vaccine Programs and Challenges”; Choh et al., “*Burkholderia* Vaccines.”

¹⁰³ Andrew Goodyear et al., “Protection from Pneumonic Infection with *Burkholderia* Species by Inhalational Immunotherapy,” *Infection and Immunity* 77, no. 4 (2009): 1579–1588.

¹⁰⁴ “Glanders Treatment,” CDC, last modified 13 January 2012, <http://www.cdc.gov/glanders/treatment/index.html>.

¹⁰⁵ Estes et al., “Therapeutic Strategies for Melioidosis and Glanders.”

species has been tested in mice, and it was found that the most efficacious antibodies were those targeting the capsule of the bacteria.¹⁰⁶

c. Animal Models

Currently, large animal models (goats and non-human primates) of *Burkholderia* species are limited to melioidosis, and their applicability to glanders is unclear.¹⁰⁷ In the absence of other alternatives, these animal models should be investigated further and compared to the existing glanders human response parameter sources.

5. Plague

a. Human Cases

Seventeen cases of plague have been reported in the United States since 2009.¹⁰⁸ The majority of cases were in rural parts of the western United States¹⁰⁹ with the notable exception of a fatal laboratory-acquired case in Chicago, in which plague was somehow contracted from an attenuated strain of *Y. pestis*.¹¹⁰ Cases of plague were also reported throughout the world, including Bolivia,¹¹¹ China,¹¹² Democratic Republic of Congo,¹¹³ Libya,¹¹⁴ Madagascar,¹¹⁵ Mongolia,¹¹⁶ Myanmar,¹¹⁷ Peru,¹¹⁸ Tanzania,¹¹⁹ and Uganda.¹²⁰

¹⁰⁶ Shimin Zhang et al., “*In Vitro* and *in Vivo* Studies of Monoclonal Antibodies with Prominent Bactericidal Activity against *Burkholderia pseudomallei* and *Burkholderia mallei*,” *Clinical and Vaccine Immunology* 18, no. 5 (2011): 825–834; Estes et al., “Therapeutic Strategies for Melioidosis and Glanders.”

¹⁰⁷ Carl Soffler et al., “Development and Characterization of a Caprine Aerosol Infection Model of Melioidosis,” *PLoS One* 7, no. 8 (2012): e43207; John J. Yeager et al., “Natural History of Inhalation Melioidosis in Rhesus Macaques (*Macaca mulatta*) and African Green Monkeys (*Chlorocebus aethiops*),” *Infection and Immunity* 80, no. 9 (2012): 3332–3340; Wolfe, Florence, and Bryant, “Biodefense Vaccine Programs and Challenges”; Choh et al., “*Burkholderia* Vaccines.”

¹⁰⁸ “Notifiable Diseases and Mortality Tables.”

¹⁰⁹ “Maps and Statistics: Plague in the United States,” CDC, last modified 23 April 2013, <http://www.cdc.gov/plague/maps/index.html>.

¹¹⁰ ProMED-mail, “Plague, Fatal—USA: (IL), 2009, Lab Strain, CDC” (ISID, 2011); CDC, “Fatal Laboratory-Acquired Infection with an Attenuated *Yersinia pestis* Strain—Chicago, Illinois, 2009,” *MMWR* 60, no. 7 (2011): 201–205; ProMED-mail, “Plague, Fatal—USA (05): (IL) Lab Strain Susp. RFI” (ISID, 2009); ProMED-mail, “Plague, Fatal—USA (04): (IL) Lab Strain Susp. RFI” (ISID, 2009).

¹¹¹ ProMED-mail, “Plague—South America: Bolivia, Peru, PAHO Report” (ISID, 2010); ProMED-mail, “Plague—Bolivia: (LP), Bubonic” (ISID, 2010).

¹¹² ProMED-mail, “Plague, Pneumonic, 2009—China: (QH) Follow Up” (ISID, 2011); H. Wang et al., “A Dog-Associated Primary Pneumonic Plague in Qinghai Province, China,” *Clin Infect Dis* 52, no. 2 (2011): 185–190; ProMED-mail, “Plague, Pneumonic—China (06): (QH), Who” (ISID, 2009); ProMED-mail, “Plague, Pneumonic—China (05): (QH) Comment” (ISID, 2009); ProMED-mail, “Plague, Pneumonic—China (04): (QH)” (ISID, 2009); ProMED-mail, “Plague, Pneumonic—China (03): (QH)” (ISID, 2009); ProMED-mail, “Plague, Pneumonic—China (02): (QH)” (ISID, 2009); ProMED-mail, “Plague, Pneumonic—China: (QH), RFI” (ISID, 2009); ProMED-mail, “Plague, Bubonic, Fatal—China: (GS)” (ISID, 2010); ProMED-mail, “Plague, Pneumonic—China: (Tibet Autonomous Region)” (ISID, 2010).

b. Medical Countermeasures

A human plague vaccine manufactured by Greer Laboratories, Inc. was licensed and used in the United States until 1999.¹²¹ Since the expiration of stored vaccines soon thereafter, a plague vaccine has not been available in the United States, but next-generation candidate vaccines are in development.¹²² In particular, F1 and V subunit vaccines have shown efficacy against both bubonic and pneumonic plague in non-human primate models,¹²³ and at least one plague rF1V vaccine candidate has undergone Phase II clinical trials.¹²⁴ Among the next steps in

¹¹³ ProMED-mail, “Plague—Congo DR: (OR)” (ISID, 2009).

¹¹⁴ ProMED-mail, “Plague, Bubonic—Libya: (BN)” (ISID, 2011); ProMED-mail, “Plague, Bubonic—Libya (02): (BN)” (ISID, 2009); ProMED-mail, “Plague, Bubonic—Libya: (BN)” (ISID, 2009).

¹¹⁵ ProMED-mail, “Plague—Madagascar (02): Fatalities” (ISID, 2012); ProMED-mail, “Plague—Madagascar: Fatalities” (ISID, 2012); ProMED-mail, “Plague, Pneumonic—Madagascar (05): (AV)” (ISID, 2011); ProMED-mail, “Plague, Pneumonic—Madagascar (04)” (ISID, 2011); ProMED-mail, “Plague, Pneumonic—Madagascar (03)” (ISID, 2011); ProMED-mail, “Plague, Pneumonic—Madagascar (02): (AS) Institut Pasteur Report” (ISID, 2011); ProMED-mail, “Plague, Pneumonic – Madagascar: (Antsiranana) RFI” (ISID, 2011).

¹¹⁶ ProMED-mail, “Plague, Pneumonic—Mongolia: (BO), RFI” (ISID, 2009).

¹¹⁷ ProMED-mail, “Plague—Myanmar: (YA)” (ISID, 2010).

¹¹⁸ ProMED-mail, “Plague—South America: Bolivia, Peru, PAHO Report”; ProMED-mail, “Plague – Bolivia: (LP), Bubonic”; ProMED-mail, “Plague—Peru (04): (LL)” (ISID, 2010); ProMED-mail, “Plague – Peru (03): (LL), PAHO” (ISID, 2010); ProMED-mail, “Plague – Peru (02): (LL), Bubonic, Pneumonic” (ISID, 2010); ProMED-mail, “Plague, Pneumonic—Peru: (TJ)” (ISID, 2010); ProMED-mail, “Plague, Bubonic – Peru: (LL), RFI” (ISID, 2010).

¹¹⁹ ProMED-mail, “Plague—Tanzania: (MY), RFI” (ISID, 2010).

¹²⁰ ProMED-mail, “Plague, Fatal—Uganda: (AW) RFI” (ISID, 2012); ProMED-mail, “Undiagnosed Disease—Uganda (07): Plague Suspected” (ISID, 2010); ProMED-mail, “Plague, Bubonic, Pneumonic—Uganda, 2006: (AW, NE)” (ISID, 2009); CDC, “Bubonic and Pneumonic Plague—Uganda, 2006,” *MMWR* 58, no. 28 (2009): 778–781; ProMED-mail, “Plague—Uganda: (AW, NE), 2008: RFI” (ISID, 2009).

¹²¹ Mary Beth Nierengarten and Larry I. Lutwick, “Vaccine Development for Plague,” *Medscape* (18 September 2002), http://www.medscape.com/viewarticle/441260_2; Hart et al., “rF1V and rBV A/B Vaccines”; Jason A. Rosenzweig et al., “Progress on Plague Vaccine Development,” *Applied Microbiology and Biotechnology* 91, no. 2 (2011): 265–286.

¹²² “Plague Prevention,” CDC, last modified 13 June 2012, <http://www.cdc.gov/plague/prevention/index.html>; Rosenzweig et al., “Progress on Plague Vaccine Development”; Lauriane E. Quenee et al., “Prevention of Pneumonic Plague in Mice, Rats, Guinea Pigs and Non-Human Primates with Clinical Grade rV10, rV10-2 or F1-V Vaccines,” *Vaccine* 29, no. 38 (2011): 6572–6583; Valentina A. Feodorova and Vladimir L. Motin, “Plague Vaccines: Current Developments and Future Perspectives,” *Emerging Microbes & Infections* 1, no. 11 (2012): e36.

¹²³ E. D. Williamson and P. C. Oyston, “Protecting against Plague: Towards a Next-Generation Vaccine,” *Clinical and Experimental Immunology* 172, no. 1 (2013): 1–8; Jessica A. Chichester et al., “A Single Component Two-Valent LcrV-F1 Vaccine Protects Non-Human Primates against Pneumonic Plague,” *Vaccine* 27, no. 25–26 (2009): 3471–3474.

¹²⁴ Williamson and Oyston, “Protecting against Plague”; Hart et al., “rF1V and rBV A/B Vaccines”; “Recombinant Plague Vaccine rF1V in Healthy Volunteers,” ClinicalTrials.gov, last modified 28 November 2011, <http://clinicaltrials.gov/show/NCT00332956>; “Randomized Single-Blinded Study to Evaluate Safety and Immunogenicity of Recombinant Plague Vaccine with and without Adjuvant,” ClinicalTrials.gov, last modified 14 August 2013, <http://clinicaltrials.gov/ct2/show/NCT01122784>.

the vaccine development process is establishing the animal model correlates of protection in humans.¹²⁵

Recent studies have investigated a number of different antibiotics to treat plague. In April 2012, the antibiotic Levaquin (levofloxacin) was approved for the treatment and post-exposure prophylaxis of plague.¹²⁶ Approval was based on a study in which Levaquin was successful in treating 16 of 17 non-human primates following inhalation exposure and subsequent fever.¹²⁷ In the same month, the FDA Anti-Infective Drugs Advisory Committee heard arguments for the approval of ciprofloxacin to treat plague,¹²⁸ but no record of their decision could be found, and a clinical trial to compare the safety and efficacy of ciprofloxacin and doxycycline to treat plague in humans was continuing to recruit patients in September 2012.¹²⁹ Although Gentamicin is used to treat plague and has been evaluated in clinical trials, it is still not indicated for this use by the FDA.¹³⁰

c. Animal Models

As it has with research on other biological agents of interest, the FDA Animal Rule has brought about a number of studies intended to establish various animal models as representative of human disease and for testing therapeutics for FDA approval. Among the recently developed animal models is a cynomolgus macaque model for pneumonic plague. A 2008 article by researchers from the Lovelace Respiratory Research Institute (LRRI) reported an inhalation LD₅₀ in cynomolgus macaques of 66 CFU,¹³¹ and another study by Battelle Biomedical Research

¹²⁵ Williamson and Oyston, “Protecting against Plague”; E. D. Williamson, “The Role of Immune Correlates and Surrogate Markers in the Development of Vaccines and Immunotherapies for Plague,” *Advances in Preventive Medicine* 2012 (2012); Feodorova and Motin, “Plague Vaccines.”

¹²⁶ “FDA Approves New Antibacterial Treatment for Plague,” FDA, last modified 5 March 2012, <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm302220.htm>.

¹²⁷ Robert Colby Layton et al., “Levofloxacin Cures Experimental Pneumonic Plague in African Green Monkeys,” *PLoS Neglected Tropical Diseases* 5, no. 2 (2011): e959.

¹²⁸ Robert Johnson, “Treatment of Pneumonic Plague: Medical Utility of Ciprofloxacin” (presentation at the Anti-Infective Drugs Advisory Committee Meeting of the National Institute of Allergy and Infectious Diseases, Silver Spring, MD, 3–4 April 2012); Katherine Laessig, “Ciprofloxacin for Pneumonic Plague” (presentation at the Anti-Infective Drugs Advisory Committee Meeting of the National Institute of Allergy and Infectious Diseases, Silver Spring, MD, 3–4 April 2012); FDA, “The Efficacy of Ciprofloxacin for Treatment of Pneumonic Plague” (briefing package, the Anti-Infective Drugs Advisory Committee Meeting of the National Institute of Allergy and Infectious Diseases, Silver Spring, MD, 3–4 April 2012).

¹²⁹ “A Clinical Trial to Evaluate the Safety and Efficacy of Ciprofloxacin in the Treatment of Plague in Humans,” ClinicalTrials.gov, last modified 10 September 2012, <http://clinicaltrials.gov/show/NCT01243437>.

¹³⁰ FDA, “African Green Monkey (*Chlorocebus aethiops*) Animal Model Development to Evaluate Treatment of Pneumonic Plague,” (briefing package, the Anti-Infective Drugs Advisory Committee Meeting of the National Institute of Allergy and Infectious Diseases, Silver Spring, MD, 3–4 April 2012); “Treatment and Diagnosis of Plague,” ClinicalTrials.gov, last modified 24 February 2009, <http://clinicaltrials.gov/show/NCT00128466>.

¹³¹ Roger Van Andel et al., “Clinical and Pathologic Features of Cynomolgus Macaques (*Macaca fascicularis*) Infected with Aerosolized *Yersinia pestis*,” *Comparative Medicine* 58, no. 1 (2008): 68–75.

Center researchers determined the LD₅₀ to be 24 CFU.¹³² Earlier studies by the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) established an LD₅₀ of 400 CFU.¹³³

As summarized in an FDA report to the Anti-Infective Drugs Advisory Committee in 2012, there were also a number of studies to establish the LD₅₀ and determine the pathology of pneumonic plague in the African green monkey.¹³⁴ According to the report, USAMRIID conducted a study to determine the LD₅₀ in this species in 1993, which was calculated to be 343 CFU¹³⁵ (more commonly reported as 350 CFU¹³⁶). Pathology results for these animals and other unvaccinated controls were later published in 1996.¹³⁷ The FDA report also cites four subsequent major studies on the pathology of pneumonic plague in African green monkeys by USAMRIID (June 2003), LRRI (April 2007 and published in 2011¹³⁸), and Battelle Biomedical Research Center (July 2007 and January 2009). Combined, these four studies exposed 36 monkeys to target doses of 100 times the LD₅₀, and all but two monkeys died.

Studies on the effectiveness of various vaccines and other therapeutics may also provide information on the infective or lethal dose, as unvaccinated controls occasionally survive supra-lethal doses. Some vaccine studies on non-human primate models have been summarized recently.¹³⁹

¹³² Richard Warren et al., “Cynomolgus Macaque Model for Pneumonic Plague,” *Microbial Pathogenesis* 50, no. 1 (2011): 12–22.

¹³³ Louise M. Pitt, “Nonhuman Primates as a Model for Pneumonic Plague,” in *Public Workshop on Animal Models and Correlates of Protection for Plague Vaccines* (Gaithersburg, MD: FDA, 2004).

¹³⁴ FDA, “African Green Monkey (*Chlorocebus aethiops*) Animal Model Development to Evaluate Treatment of Pneumonic Plague.”

¹³⁵ Pitt, “Nonhuman Primates as a Model for Pneumonic Plague”; Judy Hewitt, “African Green Monkey Model of Pneumonic Plague” (presentation at the Anti-Infective Drugs Advisory Committee Meeting of the National Institute of Allergy and Infectious Diseases, Silver Spring, MD, 3–4 April 2012).

¹³⁶ William Mega, Trevor L. Brasel, and Philip J. Kuehl, “Dissemination of Inhaled *Yersinia pestis* in the African Green Monkey Inhalational Plague Model” (Albuquerque, NM: Lovelace Respiratory Research Institute (LRRI), 2013); Layton et al., “Levofloxacin Cures Experimental Pneumonic Plague”; R. C. Layton et al., “Comparison of Two Non Human Primate Pneumonic Plague Models” (Albuquerque, NM: LRRI, 2008).

¹³⁷ K. J. Davis et al., “Pathology of Experimental Pneumonic Plague Produced by Fraction 1-Positive and Fraction 1-Negative *Yersinia pestis* in African Green Monkeys (*Cercopithecus aethiops*),” *Archives of Pathology & Laboratory Medicine* 120, no. 2 (1996): 156–163.

¹³⁸ R. Colby Layton et al., “Primary Pneumonic Plague in the African Green Monkey as a Model for Treatment Efficacy Evaluation,” *Journal of Medical Primatology* 40, no. 1 (2011): 6–17.

¹³⁹ Williamson and Oyston, “Protecting against Plague”; Williamson, “Role of Immune Correlates”; Quenee et al., “Prevention of Pneumonic Plague”; FDA, “The Efficacy of Ciprofloxacin for Treatment of Pneumonic Plague”; Y. Qiu et al., “Comparison of Immunological Responses of Plague Vaccines F1+Rv270 and EV76 in Chinese-Origin Rhesus Macaque, *Macaca mulatta*,” *Scandinavian Journal of Immunology* 72, no. 5 (2010): 425–433; Guang Tian et al., “Histopathological Observation of Immunized Rhesus Macaques with Plague Vaccines after Subcutaneous Infection of *Yersinia pestis*,” *PLoS One* 6, no. 4 (2011): e19260.

6. Q Fever

a. Human Cases

Since 2009, the CDC reported an average of approximately 130 cases of Q fever in the United States each year.¹⁴⁰ In that same period, ProMED reported human cases of Q fever in Australia,¹⁴¹ Brazil,¹⁴² Germany,¹⁴³ Hungary,¹⁴⁴ the Netherlands,¹⁴⁵ Serbia,¹⁴⁶ Spain,¹⁴⁷ and the United States.¹⁴⁸ In addition, the disease was identified as endemic in Iran,¹⁴⁹ Denmark,¹⁵⁰ and Serbia¹⁵¹ and as a recently recognized disease in Japan.¹⁵² A 2013 article also described Q fever outbreaks from 1982 to 2010 in four countries (Bulgaria, France, Germany, and the Netherlands).¹⁵³ The largest of these outbreaks was in the Netherlands from 2007 to 2010, in which 4,026 people were reportedly ill with Q fever, and a hospitalization rate of approximately 20% was reported.¹⁵⁴

b. Medical Countermeasures

The only current human vaccine for Q fever, Q-VAX, has been available since 1989,¹⁵⁵ but it is not approved for use outside of Australia.¹⁵⁶ Nevertheless, during the recent Q fever outbreaks in the Netherlands, Q-VAX was used to vaccinate populations at high risk of

¹⁴⁰ “Notifiable Diseases and Mortality Tables.”

¹⁴¹ ProMED-mail, “Q Fever—Australia: (NS)” (ISID, 2011).

¹⁴² ProMED-mail, “Q Fever—Brazil: (MG)” (ISID, 2013).

¹⁴³ ProMED-mail, “Q Fever—Germany: (NW, HE) Human, Animal” (ISID, 2011).

¹⁴⁴ ProMED-mail, “Q Fever—Hungary: (BA) RFI” (ISID, 2013).

¹⁴⁵ ProMED-mail, “Q Fever—Netherlands: Human, 2007–2010” (ISID, 2012).

¹⁴⁶ ProMED-mail, “Q Fever—Serbia: (VO)” (ISID, 2012).

¹⁴⁷ ProMED-mail, “Q Fever—Spain: (AN)” (ISID, 2013).

¹⁴⁸ ProMED-mail, “Q Fever—USA: Raw Cow's Milk, Ex Goat” (ISID, 2011).

¹⁴⁹ Ehsan Mostafavi, Hadis Rastad, and Mohammad Khalili, “Q Fever: An Emerging Public Health Concern in Iran,” *Asian Journal of Epidemiology* 5, no. 3 (2012): 66–74.

¹⁵⁰ S. Bacci et al., “Epidemiology and Clinical Features of Human Infection with *Coxiella burnetii* in Denmark During 2006–07,” *Zoonoses Public Health* 59, no. 1 (2012): 61–68.

¹⁵¹ S. Medic et al., “Q Fever Outbreak in the Village of Nocaj, Srem County, Vojvodina Province, Serbia, January to February 2012,” *Euro Surveillance* 17, no. 15 (2012).

¹⁵² Sarah Rebecca Porter et al., “Q Fever in Japan: An Update Review,” *Veterinary Microbiology* 149, no. 3–4 (2011): 298–306.

¹⁵³ M. Georgiev et al., “Q Fever in Humans and Farm Animals in Four European Countries, 1982 to 2010,” *Euro Surveillance* 18, no. 8 (2013): 13–25.

¹⁵⁴ Ibid.

¹⁵⁵ I. M. Hess et al., “Preventing Q Fever Endocarditis: A Review of Cardiac Assessment in Hospitalised Q Fever Patients,” *Rural and Remote Health* 11, no. 4 (2011): 1763.

¹⁵⁶ Georgiev et al., “Q Fever in Humans.”

developing chronic Q fever, and nearly two out of three vaccinated individuals reported adverse reactions to the vaccination.¹⁵⁷ Work on a vaccine in the United States has been ongoing, and a Phase 2 study evaluating the safety of an inactivated, freeze-dried vaccine was scheduled, but as of August 2012, the study had “suspended participant recruitment.”¹⁵⁸

The benefits of post-exposure prophylaxis following a known or suspected exposure to Q fever are not proven, so the CDC recommendation is to seek medical attention for any acute febrile illness developed within six weeks of exposure.¹⁵⁹ Doxycycline is the treatment of choice for both acute and chronic Q fever: a two week regimen for acute disease and months to years for chronic symptoms.¹⁶⁰ Doxycycline is also being evaluated as a treatment for Q fever fatigue syndrome (QFS) at Radboud University in the Netherlands.¹⁶¹

A number of articles included information that might affect the Q fever fatality or duration of illness submodels. Treated and untreated fatality rates were reported for chronic Q fever¹⁶² and for vascular complications of acute Q fever.¹⁶³ The authors of a 2009 article interviewed 54 individuals that developed Q fever in 2007 and reported that 50 of them took an absence from work or school ranging from 2 to 296 days with a median of 21 days. For the hospitalized subset of these individuals (29), the duration of hospitalization ranged from 1 to 42 days with a median of 6 days.¹⁶⁴

¹⁵⁷ Leslie D. Isken et al., “Implementation of a Q Fever Vaccination Program for High-Risk Patients in the Netherlands,” *Vaccine* 31, no. 23 (2013): 2617–2622.

¹⁵⁸ “Safety Evaluation of a Q-Fever Vaccine, NDBR 105,” ClinicalTrials.gov, last modified 21 June 2013, <http://clinicaltrials.gov/show/NCT00584454>.

¹⁵⁹ Alicia Anderson et al., “Diagnosis and Management of Q Fever—United States, 2013: Recommendations from CDC and the Q Fever Working Group,” *MMWR* 62, no. RR-03 (2013): 1–30.

¹⁶⁰ *Ibid.*

¹⁶¹ “The Qure Study: Q-Fever Fatigue Syndrome—Response to Treatment,” ClinicalTrials.gov, last modified 14 March 2013, <http://clinicaltrials.gov/show/NCT01318356>; Stephan P. Keijmel et al., “The Qure Study: Q Fever Fatigue Syndrome—Response to Treatment; a Randomized Placebo-Controlled Trial,” *BMC Infectious Diseases* 13 (2013): 157–165.

¹⁶² M. C. Wegdam-Blans et al., “Chronic Q Fever: Review of the Literature and a Proposal of New Diagnostic Criteria,” *Journal of Infection* 64, no. 3 (2012): 247–259; M. C. Wegdam-Blans et al., “Vascular Complications of Q-Fever Infections,” *European Journal of Vascular and Endovascular Surgery* 42, no. 3 (2011): 384–392.

¹⁶³ Elias E. Mazokopakis, Christos M. Karefilakis, and Ioannis K. Starakis, “Q Fever Endocarditis,” *Infectious Disorders Drug Targets* 10, no. 1 (2010): 27–31; Hess et al., “Preventing Q Fever Endocarditis.”

¹⁶⁴ Peter D. Massey, Melissa Irwin, and David N. Durrheim, “Enhanced Q Fever Risk Exposure Surveillance May Permit Better Informed Vaccination Policy,” *Communicable Diseases Intelligence Quarterly Report* 33, no. 1 (2009): 41–45.

7. Staphylococcal Enterotoxin B (SEB)

a. Human Cases

Staphylococcal enterotoxin B (SEB), often associated with food poisoning, can result in toxic shock syndrome when delivered through a nonenteric route.¹⁶⁵ Approximately 75 cases of staphylococcal toxic-shock syndrome have been reported to the U.S. CDC each year since 2009.¹⁶⁶ Typically half of these cases are menstrual-related, and the rest are caused by other factors such as skin infections, burns, and post-surgery complications.¹⁶⁷ No reports of aerosolized SEB exposure were discovered in this literature review.

b. Medical Countermeasures

Current therapy for SEB-induced toxic shock is mostly supportive care, although intravenous immunoglobulins may be effective when administered shortly after exposure.¹⁶⁸ Pre-clinical tests indicate that other therapies may also be effective in treating toxic shock syndrome. Intranasal rapamycin, an immunosuppressive drug used to prevent graft rejection, was shown to protect mice from SEB-induced toxic shock as late as 17 hours after SEB exposure.¹⁶⁹ Myeloid differentiation protein 88, MyD88, also shows promise in protecting against toxic shock syndrome caused by SEB.¹⁷⁰ Anti-SEB human monoclonal antibodies have been found to neutralize toxin *in vitro*¹⁷¹ and *in vivo* in mouse models.¹⁷² Other studies indicated that

¹⁶⁵ Robert G. Ulrich, Catherine L. Wilhelmsen, and Teresa Krakauer, "Staphylococcal Enterotoxin B and Related Toxins," in *Medical Aspects of Biological Warfare*, ed. Zygmunt F. Dembek, *Textbooks of Military Medicine* (Washington, DC: Department of Defense, Office of the Surgeon General, U.S. Army, Borden Institute, 2007), 311–322.

¹⁶⁶ "Notifiable Diseases and Mortality Tables."

¹⁶⁷ PubMed Health, "Toxic Shock Syndrome," U.S. National Library of Medicine, last modified 15 August 2012, <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001676/>.

¹⁶⁸ Teresa Krakauer and Marilyn Buckley, "Intranasal Rapamycin Rescues Mice from Staphylococcal Enterotoxin B-Induced Shock," *Toxins* 4, no. 9 (2012): 718–728; Avnish K. Varshney et al., "Generation, Characterization, and Epitope Mapping of Neutralizing and Protective Monoclonal Antibodies against Staphylococcal Enterotoxin B-Induced Lethal Shock," *Journal of Biological Chemistry* 286, no. 11 (2011): 9737–9747; Eileen A. Larkin, Bradley G. Stiles, and Robert G. Ulrich, "Inhibition of Toxic Shock by Human Monoclonal Antibodies against Staphylococcal Enterotoxin B," *PLoS One* 5, no. 10 (2010): e13253.

¹⁶⁹ Krakauer and Buckley, "Intranasal Rapamycin Rescues Mice."

¹⁷⁰ Teri L. Kissner et al., "Therapeutic Inhibition of Pro-Inflammatory Signaling and Toxicity to Staphylococcal Enterotoxin B by a Synthetic Dimeric BB-Loop Mimetic of MyD88," *PLoS One* 7, no. 7 (2012): e40773.

¹⁷¹ Eileen A. Larkin, Bradley G. Stiles, and Robert G. Ulrich, "Inhibition of Toxic Shock by Human Monoclonal Antibodies against Staphylococcal Enterotoxin B," *PLoS One* 5, no. 10 (2010): e13253; Brian Drozdowski et al., "Generation and Characterization of High Affinity Human Monoclonal Antibodies That Neutralize Staphylococcal Enterotoxin B," *Journal of Immune Based Therapies and Vaccines* 8 (2010): 9.

¹⁷² Hatice Karauzum et al., "Synthetic Human Monoclonal Antibodies toward Staphylococcal Enterotoxin B (SEB) Protective against Toxic Shock Syndrome," *Journal of Biological Chemistry* 287, no. 30 (2012): 25203–25215; Drozdowski et al., "Antibodies That Neutralize Staphylococcal Enterotoxin B."

combinations of different antibodies were more effective than a single antibody administered alone,¹⁷³ and the addition of lovastatin further increased the efficacy of treatment in one study.¹⁷⁴

A number of SEB vaccine candidates are also under development. The recombinant vaccine STEBVax, perhaps the most advanced candidate, has been shown to be efficacious in mice and non-human primates¹⁷⁵ and is currently recruiting volunteers for a Phase 1 human trial.¹⁷⁶ A soybean-derived vaccine using the same nontoxic mutant form of SEB expressed as recombinant protein in *E. coli* in the STEBVax vaccine was found to be as effective as the STEBVax vaccine in a piglet model.¹⁷⁷ An oral formulation of the STEBVax vaccine also produced an antibody response against SEB in piglets.¹⁷⁸

8. Smallpox

a. Human Cases

In 1979, the World Health Organization certified the global eradication of smallpox.¹⁷⁹ Yet more than 30 years later, smallpox is still considered a potential threat to public health, and research is ongoing to prevent and treat the disease.¹⁸⁰ Developing vaccines and therapeutics in the absence of human disease presents a challenge, which is exacerbated by the fact that humans are the only known reservoir for the smallpox virus (orthopoxvirus variola), and no single animal model is capable of perfectly modeling smallpox in humans.¹⁸¹

¹⁷³ Varshney et al., “Staphylococcal Enterotoxin B-Induced Lethal Shock”; Mulualet E. Tilahun et al., “Chimeric Anti-Staphylococcal Enterotoxin B Antibodies and Lovastatin Act Synergistically to Provide *in Vivo* Protection against Lethal Doses of SEB,” *PLoS One* 6, no. 11 (2011): e27203.

¹⁷⁴ Tilahun et al., “Chimeric Anti-Staphylococcal Enterotoxin B Antibodies.”

¹⁷⁵ Laura C. Hudson et al., “Sublethal Staphylococcal Enterotoxin B Challenge Model in Pigs to Evaluate Protection Following Immunization with a Soybean-Derived Vaccine,” *Clinical and Vaccine Immunology* 20, no. 1 (2013): 24–32; Larkin, Stiles, and Ulrich, “Antibodies against Staphylococcal Enterotoxin B”; Giselli Fernandes Asensi et al., “Oral Immunization with *Lactococcus lactis* Secreting Attenuated Recombinant Staphylococcal Enterotoxin B Induces a Protective Immune Response in a Murine Model,” *Microbial Cell Factories* 12 (2013): 32.

¹⁷⁶ “Phase I STEBVax in Healthy Adults,” ClinicalTrials.gov, last modified 31 October 2013, <http://clinicaltrials.gov/ct2/show/NCT00974935>.

¹⁷⁷ Hudson et al., “Sublethal Staphylococcal Enterotoxin B Challenge Model.”

¹⁷⁸ Tiffany K. Inskeep et al., “Oral Vaccine Formulations Stimulate Mucosal and Systemic Antibody Responses against Staphylococcal Enterotoxin B in a Piglet Model,” *Clinical and Vaccine Immunology* 17, no. 8 (2010): 1163–1169.

¹⁷⁹ “Global Alert and Response (GAR): Smallpox,” World Health Organization, accessed 24 July 2013, <http://www.who.int/csr/disease/smallpox/en/index.html>.

¹⁸⁰ M. B. Townsend et al., “Humoral Immunity to Smallpox Vaccines and Monkeypox Virus Challenge: Proteomic Assessment and Clinical Correlations,” *Journal of Virology* 87, no. 2 (2013): 900–911.

¹⁸¹ Clement A. Meseda and Jerry P. Weir, “Third-Generation Smallpox Vaccines: Challenges in the Absence of Clinical Smallpox,” *Future Microbiology* 5, no. 9 (2010): 1367–1382; Bernard Moss, “Smallpox Vaccines: Targets of Protective Immunity,” *Immunological Reviews* 239, no. 1 (2011): 8–26; Darin S. Carroll et al.,

b. Medical Countermeasures

1) Vaccines

The eradication of smallpox throughout the world was due mainly to the extensive vaccination program. The live vaccinia virus vaccines used at that time, now referred to as first-generation vaccines, included Dryvax, Aventis Pasteur Smallpox Vaccine (APSV), and Lancy-Vaxina.¹⁸² The U.S. SNS currently contains more than 300 million doses of a second-generation smallpox vaccine, ACAM2000, which has immunogenicity and safety similar to Dryvax. They were derived from the same vaccinia strain, but ACAM2000 is manufactured using more modern cell culture technology.¹⁸³ Another cell-culture derived smallpox vaccine, CJ-50300, has undergone clinical trials and was licensed by the Korean FDA in 2008.¹⁸⁴

Because ACAM2000 can have serious side effects, third-generation vaccines are being developed using two immunogenic vaccinia strains that produce comparatively milder skin lesions, LC16m8 (licensed in Japan)¹⁸⁵ and modified vaccinia Ankara (MVA).¹⁸⁶ Three MVA vaccines have been tested in humans: TBC-MVA, ACAM3000, and MVA-BN (Imvamune).¹⁸⁷ By the end of 2013, 20 million Imvamune vaccines will be available in the U.S. SNS for those unable to be vaccinated with the ACAM2000 vaccine.¹⁸⁸ Although the Imvamune vaccine is not

“Orthopoxvirus Variola Infection of *Cynomys ludovicianus* (North American Black Tailed Prairie Dog),” *Virology* 443, no. 2 (2013): 358–362.

¹⁸² Richard B. Kennedy, Inna Ovsyannikova, and Gregory A. Poland, “Smallpox Vaccines for Biodefense,” *Vaccine* 27 Suppl 4 (2009): D73–79.

¹⁸³ Russell and Gronvall, “U.S. Medical Countermeasure Development”; “First Smallpox Vaccine for Special Populations Delivered under Project BioShield,” U.S. Department of Health & Human Services, last modified 7 May 2011, <http://www.hhs.gov/news/press/2010pres/07/20100714c.html>; Moss, “Smallpox Vaccines”; Aysegul Nalca and Elizabeth E. Zumbun, “ACAM2000: The New Smallpox Vaccine for United States Strategic National Stockpile,” *Drug Design, Development and Therapy* 4 (2010): 71–79.

¹⁸⁴ Myoung-Don Oh and Jong-Koo Lee, “Milestones in History of Adult Vaccination in Korea,” *Clinical and Experimental Vaccine Research* 1, no. 1 (2012): 9–17; “Safety and Efficacy of CJ Smallpox Vaccine in Previously Vaccinated Healthy Volunteers,” ClinicalTrials.gov, last modified 30 May 2013, <http://clinicaltrials.gov/ct2/show/NCT01317238>; “Safety and Efficacy of CJ Smallpox Vaccine in Healthy Volunteers,” ClinicalTrials.gov, last modified 2 August 2011, <http://clinicaltrials.gov/show/NCT01056770>; “Safety and Efficacy of CJ-50300 in Healthy Volunteers,” ClinicalTrials.gov, last modified 7 July 2013, <http://clinicaltrials.gov/show/NCT00607243>.

¹⁸⁵ D. A. Henderson, “Smallpox Virus Destruction and the Implications of a New Vaccine,” *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science* 9, no. 2 (2011): 163–168.

¹⁸⁶ Moss, “Smallpox Vaccines.”

¹⁸⁷ Stephen R. Walsh and Raphael Dolin, “Vaccinia Viruses: Vaccines against Smallpox and Vectors against Infectious Diseases and Tumors,” *Expert Review of Vaccines* 10, no. 8 (2011): 1221–1240; Marissa B. Wilck et al., “Safety and Immunogenicity of Modified Vaccinia Ankara (ACAM3000): Effect of Dose and Route of Administration,” *Journal of Infectious Diseases* 201, no. 9 (2010): 1361–1370.

¹⁸⁸ Russell and Gronvall, “U.S. Medical Countermeasure Development”; U.S. Department of Health & Human Services, “Smallpox Vaccine for Special Populations.”

licensed,¹⁸⁹ in the case of a smallpox outbreak, the vaccine could be made available under an IND protocol.¹⁹⁰

Genetic engineering allows for the deletion of various genes with the aim of attenuating the virus without sacrificing immunogenicity.¹⁹¹ Investigational fourth-generation vaccine candidates that leverage genetic engineering include NYVAC, defective vaccinia virus Lister (dVV-L), and VACVDE3L.¹⁹² In addition to these, a dual vaccine, protective against smallpox and anthrax, has been tested on both mice and rabbits.¹⁹³

2) Therapeutics

Vaccinia immune globulin (VIG) is the only FDA approved product for treating complications from smallpox vaccinations, and it is now available in both intramuscular (IM) and IV forms.¹⁹⁴ There is also evidence that VIG administered as a post-exposure prophylaxis along with vaccination, reduces the incidence of smallpox in humans.¹⁹⁵ A secondary treatment for adverse effects of smallpox vaccination that could be used under the FDA IND protocols is cidofovir,¹⁹⁶ which has also proven effective as a post-exposure prophylaxis in rabbitpox model.¹⁹⁷ In another study, single-dose cidofovir treatments protected mice after exposure with ectromelia (mousepox) virus.¹⁹⁸ Monoclonal antibodies have also shown promise in animal models, and a cocktail of monoclonal antibodies could potentially enhance the efficacy of VIG or even replace it in the future.¹⁹⁹

¹⁸⁹ Henderson, “Smallpox Virus Destruction.”

¹⁹⁰ “Bavarian Nordic Smallpox Vaccine Facility, Denmark,” Pharmaceutical-technology.com, accessed 25 July 2013, http://www.pharmaceutical-technology.com/projects/bavarian_nordic/.

¹⁹¹ Bertram L. Jacobs et al., “Vaccinia Virus Vaccines: Past, Present and Future,” *Antiviral Research* 84, no. 1 (2009): 1–13.

¹⁹² Meseda and Weir, “Third-Generation Smallpox Vaccines”; Kennedy, Ovsyannikova, and Poland, “Smallpox Vaccines for Biodefense.”

¹⁹³ Merkel et al., “Dual Vaccine against Smallpox and Anthrax.”

¹⁹⁴ Yuhong Xiao and Stuart N. Isaacs, “Therapeutic Vaccines and Antibodies for Treatment of Orthopoxvirus Infections,” *Viruses* 2, no. 10 (2010): 2381–2403; “Medical Management of Smallpox (Vaccinia) Vaccine Adverse Reactions: Vaccinia Immune Globulin and Cidofovir,” CDC, last modified 28 September 2009, <http://emergency.cdc.gov/agent/smallpox/vaccination/mgmt-adv-reactions.asp>.

¹⁹⁵ Xiao and Isaacs, “Treatment of Orthopoxvirus Infections.”

¹⁹⁶ “Smallpox (Vaccinia) Vaccine Adverse Reactions.”

¹⁹⁷ Daniel Verreault et al., “Evaluation of Inhaled Cidofovir as Postexposure Prophylactic in an Aerosol Rabbitpox Model,” *Antiviral Research* 93, no. 1 (2012): 204–208.

¹⁹⁸ Tomer Israely et al., “A Single Cidofovir Treatment Rescues Animals at Progressive Stages of Lethal Orthopoxvirus Disease,” *Virology Journal* 9 (2012).

¹⁹⁹ Xiao and Isaacs, “Treatment of Orthopoxvirus Infections.”

Encouraging results from animal experiments have prompted human clinical trials on two antiviral drugs, CMX001 and ST-246.²⁰⁰ CMX001 was shown to prevent lethality in rabbits when used as a pre- and post-exposure prophylaxis against rabbitpox virus, although symptoms of disease were still manifest.²⁰¹ It also afforded protection as a treatment once symptoms appeared, although the effectiveness decreased the longer treatment was delayed.²⁰² Likewise, ST-246 shows potential as a prophylactic measure and treatment against aerosol exposure of orthopoxviruses and, surprisingly, may also provide additional benefits when given in combination with vaccination.²⁰³

c. Animal Models

A recent study administering the variola virus intravenously to cynomolgus macaques found that the macaque model is “an excellent surrogate for human smallpox in terms of disease onset, acute disease course, and gross and histopathological lesions.”²⁰⁴ Yet the IV route of exposure may limit the usefulness of this model for approving smallpox therapeutics in humans, and attempts at validating an aerosol model of variola virus in non-human primates were not successful.²⁰⁵

Since most animals are naturally resistant to the variola virus, related orthopoxviruses that approximate human smallpox in various animal species have been investigated, making it possible to extrapolate the effects of vaccine and antiviral candidates. Among these are the calpox virus in marmosets,²⁰⁶ rabbitpox virus in rabbits,²⁰⁷ cowpox virus in non-human

²⁰⁰ “Safety, Tolerability, Pharmacokinetics (PK) of the Anti-Orthopox Drug, ST-246 (246-Safety),” ClinicalTrials.gov, last modified 15 September 2010, <http://clinicaltrials.gov/show/NCT00907803>; “A Multicenter Open-Label Study of CMX001 Treatment of Serious Diseases or Conditions Caused by dsDNA Viruses,” ClinicalTrials.gov, last modified 28 August 2013, <http://clinicaltrials.gov/ct2/show/NCT01143181>.

²⁰¹ Amanda D. Rice et al., “Efficacy of CMX001 as a Prophylactic and Presymptomatic Antiviral Agent in New Zealand White Rabbits Infected with Rabbitpox Virus, a Model for Orthopoxvirus Infections of Humans,” *Viruses* 3, no. 2 (2011): 63–82.

²⁰² Ibid.

²⁰³ Ibid.; Aysegul Nalca et al., “Evaluation of Orally Delivered ST-246 as Postexposure Prophylactic and Antiviral Therapeutic in an Aerosolized Rabbitpox Rabbit Model,” *Antiviral Research* 79, no. 2 (2008): 121–127; Scott K. Smith et al., “Effective Antiviral Treatment of Systemic Orthopoxvirus Disease: ST-246 Treatment of Prairie Dogs Infected with Monkeypox Virus,” *Journal of Virology* 85, no. 17 (2011): 9176–9187; J. Michael Lane, “Remaining Questions About Clinical *Variola major*,” *Emerging Infectious Diseases* 17, no. 4 (2011): 676–680.

²⁰⁴ Victoria Wahl-Jensen et al., “Progression of Pathogenic Events in Cynomolgus Macaques Infected with Variola Virus,” *PLoS One* 6, no. 10 (2011): e24832.

²⁰⁵ Peter B. Jahrling et al., “Exploring the Potential of Variola Virus Infection of Cynomolgus Macaques as a Model for Human Smallpox,” *Proceedings of the National Academy of Sciences* 101, no. 42 (2004): 15196–15200.

²⁰⁶ K. Matz-Rensing et al., “The Pathology of Experimental Poxvirus Infection in Common Marmosets (*Callithrix jacchus*): Further Characterization of a New Primate Model for Orthopoxvirus Infections,” *Journal of Comparative Pathology* 146, no. 2–3 (2012): 230–242.

primates,²⁰⁸ monkeypox virus in non-human primates and prairie dogs,²⁰⁹ and vaccinia and ectromelia virus in mice.²¹⁰

9. Tularemia

a. Human Cases

Tularemia is generally believed to be a disease unique to the northern hemisphere,²¹¹ but there are recent reports of women in the Australian state of Tasmania contracting tularemia after being scratched or bitten by possums in 2011.²¹² Nevertheless, the disease is endemic in North America, Europe, and Asia,²¹³ as reflected by ProMED reports of recent cases diagnosed in Canada,²¹⁴ Germany (likely contracted in Turkey),²¹⁵ Norway,²¹⁶ Russia,²¹⁷ and Turkey.²¹⁸

²⁰⁷ Rice et al., “Efficacy of CMX001”; Nicole L. Garza et al., “Evaluation of the Efficacy of Modified Vaccinia Ankara (MVA)/IMVAMUNE against Aerosolized Rabbitpox Virus in a Rabbit Model,” *Vaccine* 27, no. 40 (2009): 5496–5504; Nalca et al., “ST-246 as Postexposure Prophylactic.”

²⁰⁸ Reed F. Johnson et al., “Cowpox Virus Infection of Cynomolgus Macaques as a Model of Hemorrhagic Smallpox,” *Virology* 418, no. 2 (2011): 102–112.

²⁰⁹ Arthur J. Goff et al., “A Novel Respiratory Model of Infection with Monkeypox Virus in Cynomolgus Macaques,” *Journal of Virology* 85, no. 10 (2011): 4898–4909; Aysegul Nalca et al., “Experimental Infection of Cynomolgus Macaques (*Macaca fascicularis*) with Aerosolized Monkeypox Virus,” *PLoS One* 5, no. 9 (2010); Ronald C. Couch and Charles H. Hobbs, “Virulence of Monkeypox Virus (Zaire Strain) Challenge Stock in Cynomolgus Macaques (*Macaca fascicularis*),” (2008); Townsend et al., “Humoral Immunity to Smallpox Vaccines”; Christina L. Hutson et al., “Monkeypox Disease Transmission in an Experimental Setting: Prairie Dog Animal Model,” *PLoS One* 6, no. 12 (2011): e28295; M. S. Keckler et al., “Establishment of the Black-Tailed Prairie Dog (*Cynomys ludovicianus*) as a Novel Animal Model for Comparing Smallpox Vaccines Administered Preexposure in Both High- and Low-Dose Monkeypox Virus Challenges,” *Journal of Virology* 85, no. 15 (2011): 7683–7698.

²¹⁰ Meseda and Weir, “Third-Generation Smallpox Vaccines”; Israely et al., “Single Cidofovir Treatment Rescues Animals”; David Esteban et al., “Mousepox, a Small Animal Model of Smallpox,” *Methods in Molecular Biology* 890 (2012): 177–198.

²¹¹ Olcay Cem Bulut et al., “Unmasked: When a Clinically Malignant Disease Turns out Infectious. A Rare Case of Tularemia,” *International Journal of Surgical Pathology* 21, no. 1 (2013): 76–81; Jeannine M. Petersen, Paul S. Mead, and Martin E. Schriefer, “*Francisella tularensis*: An Arthropod-Borne Pathogen,” *Veterinary Research* 40, no. 2 (2009): 7.

²¹² ProMED-mail, “Tularemia, Human, Possum, 2011—Australia: (TS)” (ISID, 2012); ProMED-mail, “Tularemia, Human, Possum—Australia (03): (TS)” (ISID, 2011).

²¹³ Bulut et al., “Rare Case of Tularemia”; Robert Sherwood, “Protecting Our Country against Infectious Agents,” *Breathe* 4, no. 1 (2011): 8–12.

²¹⁴ ProMED-mail, “Tularemia, Pneumonic—Canada: (AB) Biologic Immunomodulator” (ISID, 2012).

²¹⁵ ProMED-mail, “Tularemia, Imported—Germany: (Berlin) Ex Turkey, Alert” (ISID, 2011).

²¹⁶ ProMED-mail, “Tularemia—Norway (02): (Central)” (ISID, 2011).

²¹⁷ ProMED-mail, “Tularemia—Russia (02): (KM)” (ISID, 2013).

²¹⁸ Kadriye Serife Ugur et al., “Three Cases of Oropharyngeal Tularemia in Turkey,” *Auris Nasus Larynx* 38, no. 4 (2011): 532–537.

Tularemia is also endemic in the United States, with an average of more than 130 cases of tularemia reported to the CDC annually from 2009 to 2012.²¹⁹ Arkansas, Oklahoma, and Missouri account for approximately 40% of tularemia cases in the United States each year.²²⁰ Of the 190 tularemia cases in Missouri reported from 2000 to 2007, clinical records were available for 121 and were summarized in two articles.²²¹ The reports documented the incubation periods (ranging from one to nine days with a median of three days)²²² and clinical forms of the disease (including 26 pneumonic cases with six known inhalational exposures),²²³ but the comprehensive dataset specifying incubation periods for pneumonic tularemia patients was not published. Since the combined data are not available and the exposures were not of known doses, these data are less useful for developing an incubation period submodel than the human exposure data from the tularemia MRV experiments currently used in *AMedP-8(C)*.

b. Medical Countermeasures

While a number of antibiotics have been proven effective in treating tularemia,²²⁴ there is still no tularemia vaccine licensed for general use in the United States.²²⁵ A live vaccine strain (LVS), developed by the Soviet Union and gifted to the United States in 1956, at one point had IND status.²²⁶ Yet today the vaccine is used only for at-risk military and laboratory personnel.²²⁷ The LVS vaccine has proven to be effective in reducing the incidence of laboratory-acquired tularemia,²²⁸ has protected nonhuman primates challenged with high aerosol doses,²²⁹ and has

²¹⁹ “Notifiable Diseases and Mortality Tables.”

²²⁰ G. Turabelidze et al., “Tularemia—Missouri, 2000–2007,” *MMWR* 58, no. 27 (2009): 744–748.

²²¹ Ingrid B. Weber et al., “Clinical Recognition and Management of Tularemia in Missouri: A Retrospective Records Review of 121 Cases,” *Clinical Infectious Diseases* 55, no. 10 (2012): 1283–1290; Turabelidze et al., “Tularemia—Missouri, 2000–2007.”

²²² Weber et al., “Clinical Recognition and Management of Tularemia.”

²²³ Turabelidze et al., “Tularemia—Missouri, 2000–2007.”

²²⁴ Nada S. Harik, “Tularemia: Epidemiology, Diagnosis, and Treatment,” *Pediatric Annals* 42, no. 7 (2013): 288–292; George G. A. Pujalte and Joel V. Chua, “Tick-Borne Infections in the United States,” *Primary Care* 40, no. 3 (2013): 619–635; Weber et al., “Clinical Recognition and Management of Tularemia.”

²²⁵ J. Wayne Conlan, “Tularemia Vaccines: Recent Developments and Remaining Hurdles,” *Future Microbiology* 6, no. 4 (2011): 391–405. Michael J. Parmely, Jeffrey L. Fischer, and David M. Pinson, “Programmed Cell Death and the Pathogenesis of Tissue Injury Induced by Type A *Francisella tularensis*,” *FEMS Microbiology Letters* 301, no. 1 (2009): 1–11.

²²⁶ Roger D. Pechous, Travis R. McCarthy, and Thomas C. Zahrt, “Working toward the Future: Insights into *Francisella tularensis* Pathogenesis and Vaccine Development,” *Microbiology and Molecular Biology Reviews* 73, no. 4 (2009): 684–711; Eileen M. Barry, Leah E. Cole, and Araceli E. Santiago, “Vaccines against Tularemia,” *Human Vaccines* 5, no. 12 (2009): 832–838.

²²⁷ Julie A. Wilder et al., “Cellular and Humoral Immune Response of Cynomolgus Macaques to *Francisella tularensis* LVS and SCHU S4 Antigens” (Albuquerque, NM: LRRI, 2009); Pechous, McCarthy, and Zahrt, “*Francisella tularensis* Pathogenesis”; Sherwood, “Protecting Our Country.”

²²⁸ Barry, Cole, and Santiago, “Vaccines against Tularemia.”

undergone human clinical studies.²³⁰ Nevertheless, the fact that the LVS vaccine is based on an attenuated Type B strain of *F. tularensis* and only partially protects against virulent Type A challenge, among other drawbacks, has led to further investigation into alternative tularemia vaccines.²³¹ A number of vaccine candidates (acellular subunit, killed whole cell, and live attenuated vaccines) have been developed and tested in mice,²³² and two are also being tested in nonhuman primate models at LRRI.²³³ Studies indicate that respiratory vaccination may be the best protector against aerosol challenge.²³⁴

c. Animal Models

Nonhuman primate studies on tularemia have been conducted on at least three species. Investigations with rhesus macaques were conducted in the 1960s and 1970s, and more recently models have been validated in African green monkeys (at USAMRIID) and cynomolgus macaques (at LRRI).²³⁵ The cynomolgus macaque LD₅₀ for tularemia was 1–2 CFU,²³⁶ and a relationship between dose and time to death was found in this species, which may be useful to developing a dose-dependent time-to-death model for humans.²³⁷ No such relationship was found in the five African green monkeys exposed at USAMRIID.²³⁸

²²⁹ Michelle Valderas et al., “Telemetry Characterization of *F. tularensis* SCHU S4 Aerosol Infection with Naive and LVS Vaccinated Cynomolgus Macaques” (Albuquerque, NM: LRRI, 2011). Robert Sherwood et al., “Growth Media Affects *Francisella tularensis* SCHU S4 Virulence in Aerosol Challenged LVS-Vaccinated Cynomolgus Macaques” (Albuquerque, NM: LRRI, 2011).

²³⁰ “Safety and Immunogenicity Study of a Live *Francisella tularensis* Vaccine,” ClinicalTrials.gov, last modified 8 August 2012, <http://clinicaltrials.gov/show/NCT00584844>; “Continued Safety and Immunogenicity Study of a Live *Francisella tularensis* Vaccine,” ClinicalTrials.gov, last modified 27 August 2013, <http://clinicaltrials.gov/show/NCT00787826>; “Phase II Tularemia Vaccine Comparison,” ClinicalTrials.gov, last modified 29 August 2013, <http://clinicaltrials.gov/ct2/show/NCT01150695>.

²³¹ Barry, Cole, and Santiago, “Vaccines against Tularemia.”

²³² Conlan, “Tularemia Vaccines”; Pechous, McCarthy, and Zahrt, “*Francisella tularensis* Pathogenesis”; Barry, Cole, and Santiago, “Vaccines against Tularemia.”

²³³ Sherwood, “Protecting Our Country.”

²³⁴ Pechous, McCarthy, and Zahrt, “*Francisella tularensis* Pathogenesis.”

²³⁵ N. A. Twenhafel, D. A. Alves, and B. K. Purcell, “Pathology of Inhalational *Francisella tularensis* Spp. *tularensis* SCHU S4 Infection in African Green Monkeys (*Chlorocebus aethiops*),” *Veterinary Pathology* 46, no. 4 (2009): 698–706; Michelle Wright Valderas et al., “Natural History Characterization of Aerosol Infection of Cynomolgus Macaques with *F. tularensis* SCHU S4” (Albuquerque, NM: LRRI, 2010); Wilder et al., “Cellular and Humoral Immune Response of Cynomolgus Macaques to *Francisella tularensis* LVS and SCHU S4 Antigens.”

²³⁶ Valderas et al., “Natural History Characterization of Aerosol Infection of Cynomolgus Macaques with *F. tularensis* SCHU S4”; Michelle Wright Valderas et al., “Determination of the *Francisella tularensis* SCHU S4 Aerosol LD50 in Cynomolgus Macques and Characterization of Tularemia Manifestation” (Albuquerque, NM: LRRI, 2009).

²³⁷ Valderas et al., “Determination of the *Francisella tularensis* SCHU S4 Aerosol LD50 in Cynomolgus Macques and Characterization of Tularemia Manifestation.”

²³⁸ Twenhafel, Alves, and Purcell, “Pathology of Inhalational *Francisella tularensis*.”

10. Venezuelan Equine Encephalitis (VEE)

a. Human Cases

Since 2009, ProMED has reported cases of Venezuelan equine encephalitis (VEE) in Belize,²³⁹ Panama,²⁴⁰ and Venezuela²⁴¹ and one suspected case in Columbia.²⁴² Although VEE is not on the U.S. CDC list of notifiable diseases,²⁴³ there was no indication on PubMed or the CDC website that there were any recent cases of VEE in the United States. The CDC does, however, have recorded cases of the related alphaviruses eastern equine encephalitis (EEE) and western equine encephalitis (WEE); since the beginning of 2009, there were 36 EEE cases and no WEE cases reported.²⁴⁴

b. Medical Countermeasures

Although there are currently no VEE vaccines or antiviral drugs that are licensed for use in humans,²⁴⁵ a live-attenuated vaccine, TC-83, and a formalin-inactivated variant of TC-83, C-84, have been used for decades in the United States to protect laboratory workers and other at-risk personnel under IND protocols.²⁴⁶ Due to concerns over the safety and immunogenicity of these vaccines, there has been considerable effort to develop next generation vaccines.²⁴⁷

²³⁹ Antonio E. Muniz, “Venezuelan Equine Encephalitis in a Teenager Visiting Central America,” *Pediatric Emergency Care* 28, no. 4 (2012): 372–375.

²⁴⁰ ProMED-mail, “Venezuelan Equine Encephalitis—Panama (03): (DR) Fatal” (ISID, 2010); ProMED-mail, “Venezuelan Equine Encephalitis—Panama (02): (DR) Fatal” (ISID, 2010); ProMED-mail, “Venezuelan Equine Encephalitis—Panama: (DR) Fatal” (ISID, 2010).

²⁴¹ ProMED-mail, “Venezuelan Equine Encephalitis—Venezuela: Humans, Equines” (ISID, 2010).

²⁴² ProMED-mail, “Venezuelan Equine Encephalitis—Columbia Ex Venezuela (ZU) Susp.” (ISID, 2013).

²⁴³ CDC, “Summary of Notifiable Diseases—United States, 2011,” *MMWR* 60, no. 53 (2013).

²⁴⁴ “Notifiable Diseases and Mortality Tables.”

²⁴⁵ Svetlana Atasheva et al., “Pseudoinfectious Venezuelan Equine Encephalitis Virus: A New Means of Alphavirus Attenuation,” *Journal of Virology* 87, no. 4 (2013): 2023–2035; K. E. Steele and N. A. Twenhafel, “Review Paper: Pathology of Animal Models of Alphavirus Encephalitis,” *Veterinary Pathology* 47, no. 5 (2010): 790–805; Lesley C. Dupuy et al., “Immunogenicity and Protective Efficacy of a DNA Vaccine against Venezuelan Equine Encephalitis Virus Aerosol Challenge in Nonhuman Primates,” *Vaccine* 28, no. 46 (2010): 7345–7350; Amanda J. Williams et al., “Improved Efficacy of a Gene Optimised Adenovirus-Based Vaccine for Venezuelan Equine Encephalitis Virus,” *Virology Journal* 6 (2009): 118.

²⁴⁶ Donald L. Fine et al., “A Multisystem Approach for Development and Evaluation of Inactivated Vaccines for Venezuelan Equine Encephalitis Virus (VEEV),” *Journal of Virological Methods* 163, no. 2 (2010): 424–432; Dupuy et al., “Efficacy of a DNA Vaccine”; Williams et al., “Gene Optimised Adenovirus-Based Vaccine”; Atasheva et al., “Pseudoinfectious Venezuelan Equine Encephalitis Virus.”

²⁴⁷ Fine et al., “Development and Evaluation of Inactivated Vaccines”; Dupuy et al., “Efficacy of a DNA Vaccine”; Williams et al., “Gene Optimised Adenovirus-Based Vaccine”; Atasheva et al., “Pseudoinfectious Venezuelan Equine Encephalitis Virus.”

Among the various vaccine candidates are live-attenuated vaccines such as V3526, which proved efficacious in animals but caused adverse effects in Phase 1 human clinical trials.²⁴⁸ Although attenuated vaccines are typically highly immunogenic, most rely on serial passage of a virulent virus strain through a culture medium (83 passages for TC-83),²⁴⁹ which introduces a few point mutations that could potentially revert back to the virulent strain upon virus replication.²⁵⁰ To overcome these shortcomings, several vaccine candidates have been developed that combine VEE virus structures with those from other viruses, such as Sindbus virus chimeric,²⁵¹ encephalomyocarditis virus,²⁵² and adenoviruses.²⁵³ In addition, formalin-inactivated and gamma irradiation-inactivated versions of V3526 (fV3526 and gV3526, respectively) have been tested in mouse models and shown to be at least as efficacious as C-84.²⁵⁴ Other vaccine candidates include DNA vaccines²⁵⁵ and pseudoinfectious virus (PIV) vaccines.²⁵⁶

In addition to vaccine research, other areas of medical countermeasure development have seen progress. Most notably, mouse monoclonal antibodies have been shown to protect mice from aerosol and subcutaneous challenge with VEE virus, although the antibodies would need to be “humanized” before being used in humans.²⁵⁷

²⁴⁸ Fine et al., “Development and Evaluation of Inactivated Vaccines”; Williams et al., “Gene Optimised Adenovirus-Based Vaccine.”

²⁴⁹ Dupuy et al., “Efficacy of a DNA Vaccine.”

²⁵⁰ Atasheva et al., “Pseudoinfectious Venezuelan Equine Encephalitis Virus”; Shannan L. Rossi et al., “IRES-Based Venezuelan Equine Encephalitis Vaccine Candidate Elicits Protective Immunity in Mice,” *Virology* 437, no. 2 (2013): 81–88.

²⁵¹ Rossi et al., “IRES-Based Venezuelan Equine Encephalitis Vaccine”; Dupuy et al., “Efficacy of a DNA Vaccine.”

²⁵² Rossi et al., “IRES-Based Venezuelan Equine Encephalitis Vaccine.”

²⁵³ Williams et al., “Gene Optimised Adenovirus-Based Vaccine”; Lyn O'Brien et al., “Alpha Interferon as an Adenovirus-Vectored Vaccine Adjuvant and Antiviral in Venezuelan Equine Encephalitis Virus Infection,” *Journal of General Virology* 90, no. Pt 4 (2009): 874–882.

²⁵⁴ Fine et al., “Development and Evaluation of Inactivated Vaccines”; Shannon S. Martin et al., “Evaluation of Formalin Inactivated V3526 Virus with Adjuvant as a Next Generation Vaccine Candidate for Venezuelan Equine Encephalitis Virus,” *Vaccine* 28, no. 18 (2010): 3143–3151.

²⁵⁵ Lesley C. Dupuy et al., “A DNA Vaccine for Venezuelan Equine Encephalitis Virus Delivered by Intramuscular Electroporation Elicits High Levels of Neutralizing Antibodies in Multiple Animal Models and Provides Protective Immunity to Mice and Nonhuman Primates,” *Clinical and Vaccine Immunology* 18, no. 5 (2011): 707–716; Dupuy et al., “Efficacy of a DNA Vaccine”; Lesley C. Dupuy et al., “Directed Molecular Evolution Improves the Immunogenicity and Protective Efficacy of a Venezuelan Equine Encephalitis Virus DNA Vaccine,” *Clinical and Vaccine Immunology* 27, no. 31 (2009): 4152–4160; Slobodan Paessler and Scott C. Weaver, “Vaccines for Venezuelan Equine Encephalitis,” *Clinical and Vaccine Immunology* 27 Suppl 4: D80–85.

²⁵⁶ Atasheva et al., “Pseudoinfectious Venezuelan Equine Encephalitis Virus.”

²⁵⁷ Lyn M. O'Brien et al., “Development of a Novel Monoclonal Antibody with Reactivity to a Wide Range of Venezuelan Equine Encephalitis Virus Strains,” *Virology Journal* 6 (2009): 206.

C. Chemical Agents

1. Distilled Mustard (HD)

a. Human Cases

While the United States nears completion of the destruction of its chemical weapons stockpiles,²⁵⁸ elsewhere in the world, chemical agents are still a battlefield threat. The Syrian military, for instance, is known to have stockpiles of chemical agents, including HD,²⁵⁹ and both sides in the ongoing civil war have confirmed the use of chemical nerve agents.²⁶⁰

Although chemical agent attacks with HD have not been reported in Syria, other recent exposures to HD have been confirmed. In March 2013, it was reported that 20 guards in Libya were exposed to HD while securing a chemical weapons storage facility. The guards were transported to Europe for specialized treatment, but the extent of their injuries is unknown.²⁶¹

In 2010 and 2012, U.S. commercial fishermen dredging for clams discovered discarded munitions filled with HD. In the 2010 incident, one of the fishermen was admitted to the hospital for five days and had multiple lesions on his skin, while another man was evaluated and released.²⁶² In the 2012 episode, none of the potentially exposed individuals developed symptoms of mustard poisoning.²⁶³

In addition to these more recent experiences, the literature review revealed a number of review articles that summarized the physiological effects of HD exposure and the current knowledge of its mechanisms of action and potential treatment options.²⁶⁴ In addition, several

²⁵⁸ “Army Agency Completes Mission to Destroy Chemical Weapons,” U.S. Army Chemical Materials Agency, last modified 23 January 2012, <http://www.cma.army.mil/fndocumentviewer.aspx?DocID=003683880>.

²⁵⁹ Melissa Block, “Syria’s Chemical Weapons Include Sarin, Mustard Gas,” *National Public Radio* (7 December 2012), <http://www.npr.org/2012/12/07/166755923/syrias-chemical-weapons-include-sarin-mustard-gas>; Andre de Nesnera, “Experts Assess Syria’s Chemical Weapons Capabilities,” *Voice of America* (25 April 2013), <http://www.voanews.com/content/syria-chemicals-weapons/1649156.html>.

²⁶⁰ Damien McElroy, “France Says It Is ‘Certain’ That Assad Regime Has Used Sarin Gas in Syria,” *The Telegraph* (4 June 2013), <http://www.telegraph.co.uk/news/worldnews/middleeast/syria/10099342/France-says-it-is-certain-that-Assad-regime-has-used-sarin-gas-in-Syria.html>; Peter James Spielmann and Edith M. Lederer, “Russia: Syrian Rebels Made, Used Sarin Nerve Gas,” *Yahoo! News* (9 July 2013), <http://news.yahoo.com/russia-syrian-rebels-made-used-sarin-nerve-gas-165341940.html>.

²⁶¹ Ashraf Abdul-Wahab, “20 Security Guards Suffer Mustard Gas Poisoning,” *Libya Herald* (23 March 2013), <http://www.libyaherald.com/2013/03/23/20-security-guards-suffer-mustard-gas-poisoning/#axzz2fFesiqeX>.

²⁶² Russell Fendick et al., “Notes from the Field: Exposures to Discarded Sulfur Mustard Munitions—Mid-Atlantic and New England States 2004–2012,” *MMWR* 62, no. 16 (2013): 315–316; Kathryn Weibrecht et al., “Sulfur Mustard Exposure Presenting to a Community Emergency Department,” *Annals of Emergency Medicine* 59, no. 1 (2012): 70–74.

²⁶³ Fendick et al., “Exposures to Discarded Sulfur Mustard Munitions.”

²⁶⁴ Feng Ru Tang and Weng Keong Loke, “Sulfur Mustard and Respiratory Diseases,” *Critical Reviews in Toxicology* 42, no. 8 (2012): 688–702; Hamid Saber, Amin Saburi, and Mostafa Ghanei, “Clinical and

studies have investigated the long-term sequelae of HD exposure in military and civilian populations exposed in the Iran-Iraq War in the 1980s.²⁶⁵ The molecular pathogenesis of HD injury is incomplete, but the current knowledge is well summarized in these review articles.²⁶⁶

b. Medical Countermeasures

Although there is no specific antidote for HD poisoning,²⁶⁷ a number of reports have identified potential therapeutics for cutaneous lesions resulting from HD exposure. One article categorized countermeasure approaches into six strategies: intracellular scavengers, DNA cell cycle modulators, PARP inhibitors, calcium modulators, protease inhibitors, and anti-inflammatory compounds.²⁶⁸ This article also identified 19 candidate countermeasures with greater than 50% efficacy in the mouse ear vesicant model, which fell into four of the six pharmacologic strategies mentioned above (all except DNA cell cycle modulators and calcium modulators). In addition, antioxidant therapies,²⁶⁹ iodine,²⁷⁰ and baicalin²⁷¹ have reportedly demonstrated some therapeutic benefits in treating cutaneous mustard lesions.

Paraclinical Guidelines for Management of Sulfur Mustard Induced Bronchiolitis Obliterans; from Bench to Bedside,” *Inhalation Toxicology* 24, no. 13 (2012): 900–906; Kamyar Ghabili et al., “Sulfur Mustard Toxicity: History, Chemistry, Pharmacokinetics, and Pharmacodynamics,” *Critical Reviews in Toxicology* 41, no. 5 (2011): 384–403; Kamyar Ghabili et al., “Mustard Gas Toxicity: The Acute and Chronic Pathological Effects,” *Journal of Applied Toxicology* 30, no. 7 (2010): 627–643; Mostafa Ghanei et al., “Acute and Chronic Effects of Sulfur Mustard on the Skin: A Comprehensive Review,” *Cutaneous and Ocular Toxicology* 29, no. 4 (2010): 269–277.

²⁶⁵ Mostafa Ghanei et al., “Long-Term Pulmonary Complications of Chemical Warfare Agent Exposure in Iraqi Kurdish Civilians,” *Inhalation Toxicology* 22, no. 9 (2010): 719–724; Mostafa Ghanei and Ali Amini Harandi, “Lung Carcinogenicity of Sulfur Mustard,” *Clinical Lung Cancer* 11, no. 1 (2010): 13–17; M. R. Sedghipour et al., “The Ocular Complications of Mustard Gas Poisoning and Their Association with the Respiratory System Involvement: An Experience in 112 Iranian Veterans,” *Cutaneous and Ocular Toxicology* 31, no. 1 (2012): 48–52; Yunes Panahi et al., “Management of Sulfur Mustard-Induced Chronic Pruritus: A Review of Clinical Trials,” *Cutaneous and Ocular Toxicology* 31, no. 3: 220–225.

²⁶⁶ Ghabili et al., “Sulfur Mustard Toxicity”; K. Kehe et al., “Molecular Toxicology of Sulfur Mustard-Induced Cutaneous Inflammation and Blistering,” *Toxicology* 263, no. 1 (2009): 12–19; Michael P. Shakarjian et al., “Mechanisms Mediating the Vesicant Actions of Sulfur Mustard after Cutaneous Exposure,” *Toxicological Sciences* 114, no. 1 (2010): 5–19.

²⁶⁷ R. Pita and S. Vidal-Asensi, “Cutaneous and Systemic Toxicology of Vesicant (Blister) Warfare Agents,” *Actas Dermo-Sifiliográficas* 101, no. 1 (2010): 7–18; A. Gautam and R. Vijayaraghavan, “Drde-07: A Possible Antidote for Sulphur Mustard Toxicity,” *Cellular and Molecular Biology* 56 Suppl (2010): OL1334–1340.

²⁶⁸ William J. Smith, “Therapeutic Options to Treat Sulfur Mustard Poisoning—the Road Ahead,” *Toxicology* 263, no. 1 (2009): 70–73.

²⁶⁹ M. Pohanka, “Antioxidants Countermeasures against Sulfur Mustard,” *Mini Reviews in Medicinal Chemistry* 12, no. 8 (2012): 742–748.

²⁷⁰ Zohreh Poursaleh et al., “Pathogenesis and Treatment of Skin Lesions Caused by Sulfur Mustard,” *Cutaneous and Ocular Toxicology* 31, no. 3 (2012): 241–249; Shakarjian et al., “Vesicant Actions of Sulfur Mustard.”

²⁷¹ A. Sahebkar, “Baicalin as a Potentially Promising Drug for the Management of Sulfur Mustard Induced Cutaneous Complications: A Review of Molecular Mechanisms,” *Cutaneous and Ocular Toxicology* 31, no. 3 (2012): 226–234.

2. Sarin (G) and Methylphosphonothioic Acid (VX)

a. Human Cases

Sarin and VX are nerve agents that were stockpiled by many countries during or after WWII.²⁷² Sarin is the chemical or biological agent most recently reported to have been used in warfare. In June 2013, France, the United States, and the United Nations reported that the regime of Syrian President Bashar al-Assad used sarin in the Syrian civil war and was responsible for an estimated 100 to 150 nerve agent casualties.²⁷³ In a July 2013 statement, the Russian ambassador to the United Nations asserted that Syrian rebels were responsible for using sarin in an attack that killed at least 26 in March 2013.²⁷⁴

b. Medical Countermeasures

The majority of the peer-reviewed literature related to sarin and VX focuses on therapeutic advancements. The standard treatment for nerve agent poisoning consists of atropine, an oxime (2-PAM in the United States), and an anticonvulsant (diazepam in the United States), but replacements or adjuncts for each of these components of therapy are being developed or tested. For instance, atropine combined with galantamine protected mice even when treatment was delayed until 30 to 45 minutes post-exposure.²⁷⁵ A number of new oximes are also under investigation. HI-6 and MMB-4 have been proposed as replacements for the currently fielded oxime 2-PAM.²⁷⁶ Other potential oximes of interest include scopolamine,²⁷⁷ TAB2OH,²⁷⁸

²⁷² Frederick R. Sidell, Jonathan Newmark, and John H. McDonough, "Nerve Agents," in *Medical Aspects of Chemical Warfare*, ed. Shirley D. Tuorinsky, *Textbooks of Military Medicine* (Washington, DC: Department of Defense, Office of the Surgeon General, U.S. Army, Borden Institute, 2008), 155–219.

²⁷³ McElroy, "Assad Regime Has Used Sarin Gas"; Margaret Besheer, "UN, France Allege Chemical Weapons Use in Syria," *GlobalSecurity.org* (4 June 2013), <http://www.globalsecurity.org/wmd/library/news/syria/2013/syria-130604-voa03.htm>; Debora MacKenzie, "Syria Has Crossed Chemical Red Line, Says Obama," *New Scientist* (14 June 2013), <http://www.newscientist.com/article/dn23704-syria-has-crossed-chemical-red-line-says-obama.html#.ubtiqee-2S0>.

²⁷⁴ Spielmann and Lederer, "Russia: Syrian Rebels Made, Used Sarin Nerve Gas"; Arthur Bright, "Russian Report Says Sarin Used in Syria – by Rebels," *Christian Science Monitor* (10 July 2013), <http://www.csmonitor.com/World/terrorism-security/2013/0710/Russian-report-says-sarin-used-in-Syria-by-rebels>; "Russia Claims Syria Rebels Used Sarin at Khan Al-Assal," *British Broadcasting Corporation* (9 July 2013), <http://www.bbc.co.uk/news/world-middle-east-23249104>.

²⁷⁵ Edna F. R. Pereira et al., "Molecular and Cellular Actions of Galantamine: Clinical Implications for Treatment of Organophosphorus Poisoning," *Journal of Molecular Neuroscience* 40, no. 1-2 (2010): 196–203.

²⁷⁶ Paul M. Lundy et al., "Comparative Protective Effects of HI-6 and MMB-4 against Organophosphorous Nerve Agent Poisoning," *Toxicology* 285, no. 3 (2011): 90–96.

²⁷⁷ I. Koplovitz and S. Schulz, "Perspectives on the Use of Scopolamine as an Adjunct Treatment to Enhance Survival Following Organophosphorus Nerve Agent Poisoning," *Military Medicine* 175, no. 11 (2010): 878–882.

K027,²⁷⁹ and K203.²⁸⁰ Tertiary oximes, such as monoisonitrosoacetone (MINA), diacetylmonoxime (DAM), and pro-2-PAM are capable of reactivating acetylcholinesterase in the central nervous system and are therefore more effective at preventing seizures than the quaternary oximes 2-PAM, HLö7, and MMB-4.²⁸¹ In 2006, a Phase 1 trial was completed testing midazolam as a potential anticonvulsant replacement for diazepam.²⁸²

For percutaneous VX, topical skin barrier creams can be used as a form of pretreatment to reduce the amount of agent absorbed. A number of such skin protectants have been tested *in vitro* and some have begun safety testing in humans.²⁸³

Experiments with bioscavengers as alternatives to traditional nerve agent treatment are also being reported. A human serum butyrylcholinesterase was tested in rats²⁸⁴ and completed Phase 1 human trials in 2008 for both IM and IV administration.²⁸⁵ In 2009, a recombinant human

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- ²⁷⁸ Zoran Radic et al., “Catalytic Detoxification of Nerve Agent and Pesticide Organophosphates by Butyrylcholinesterase Assisted with Non-Pyridinium Oximes,” *Biochemical Journal* 450, no. 1 (2013): 231–242.
- ²⁷⁹ Kamil Kuca et al., “Oxime K027: Novel Low-Toxic Candidate for the Universal Reactivator of Nerve Agent- and Pesticide-Inhibited Acetylcholinesterase,” *Journal of Enzyme Inhibition and Medicinal Chemistry* 25, no. 4 (2010): 509–512.
- ²⁸⁰ J. Kassa et al., “Two Possibilities How to Increase the Efficacy of Antidotal Treatment of Nerve Agent Poisonings,” *Mini-Reviews in Medicinal Chemistry* 12, no. 1 (2012): 24–34; Jiri Kassa et al., “The Benefit of Combinations of Oximes for the Reactivating and Therapeutic Efficacy of Antidotal Treatment of Sarin Poisoning in Rats and Mice,” *Basic & Clinical Pharmacology & Toxicology* 109, no. 1 (2011): 30–34; Jiří Kassa et al., “A Comparison of the Reactivating and Therapeutic Efficacy of the Newly Developed Bispyridinium Oxime K203 with Currently Available Oximes, in Sarin Poisoned Rats and Mice,” *Journal of Applied Biomedicine* 9, no. 4 (2011): 225–230.
- ²⁸¹ Tsung-Ming Shih et al., “Treatment with Tertiary Oximes Prevents Seizures and Improves Survival Following Sarin Intoxication,” *Journal of Molecular Neuroscience* 40, no. 1-2 (2010): 63–69; Tsung-Ming Shih et al., “The Oxime pro-2-PAM Provides Minimal Protection against the CNS Effects of the Nerve Agents Sarin, Cyclosarin, and VX in Guinea Pigs,” *Toxicology Mechanisms and Methods* 21, no. 1 (2011): 53–62; James C. Demar et al., “Pro-2-PAM Therapy for Central and Peripheral Cholinesterases,” *Chemico-Biological Interactions* 187, no. 1–3 (2010): 191–198.
- ²⁸² “Phase I Trial for Intramuscular Administration of Midazolam Using an Autoinjector (AAS),” ClinicalTrials.gov, last modified 21 September 2007, <http://www.clinicaltrials.gov/ct2/show/NCT00534378>.
- ²⁸³ J. Millerioux et al., “*In Vitro* Selection and Efficacy of Topical Skin Protectants against the Nerve Agent VX,” *Toxicology In Vitro* 23, no. 3 (2009): 539–545; J. Millerioux et al., “Evaluation of *in Vitro* Tests to Assess the Efficacy of Formulations as Topical Skin Protectants against Organophosphorus Compounds,” *Toxicology In Vitro* 23, no. 1: 127–133; Arik Eisenkraft et al., “Phase I Study of a Topical Skin Protectant against Chemical Warfare Agents,” *Military Medicine* 174, no. 1 (2009): 47–52.
- ²⁸⁴ Raymond F. Genovese et al., “Safety of Administration of Human Butyrylcholinesterase and Its Conjugates with Soman or VX in Rats,” *Basic & Clinical Pharmacology & Toxicology* 106, no. 5 (2010): 428–434.
- ²⁸⁵ “A Study of Plasma-Derived Human Butyrylcholinesterase Administered Intramuscularly,” ClinicalTrials.gov, last modified 13 January 2009, <http://www.clinicaltrials.gov/ct2/show/NCT00333528>; “Pharmacokinetic (PK) and Safety Study of Plasma-Derived Human Butyrylcholinesterase Administered Intravenously,” ClinicalTrials.gov, last modified 13 January 2009, <http://www.clinicaltrials.gov/ct2/show/NCT00333515>.

butyrylcholinesterase, Protexia, completed a Phase 1 clinical trial.²⁸⁶ Catalytic bioscavengers such as organophosphorus hydrolase (OPH)²⁸⁷ and paraoxonase 1 are also being investigated for protection against nerve agent toxicity.²⁸⁸

Other forms of treatment include tropicamide, a topical anticholinergic drug, which was reported to decrease miosis without the side effects of atropine or homatropine (“mydriasis and partial cycloplegia, which may worsen visual performance”).²⁸⁹ Another article emphasized the need to consider delayed treatments, such as brain cell therapy, neuroregeneration, and cytokine cocktail treatment, to repair nerve agent-induced brain lesions.²⁹⁰

D. Radiation

1. Human Cases

Perhaps the most noteworthy radiological event since 2009 was the Fukushima Daiichi nuclear disaster in Japan on 11 March 2011. Although large amounts of radioactive material were released from the power plant into the environment, nobody was reported to have received doses high enough to cause acute radiation syndrome (ARS).²⁹¹ In contrast, other recent radiation accidents have resulted in symptoms and even death. In 2010, seven people were hospitalized after accidental exposure to ⁶⁰Co in a pile of scrap metal in India, one of whom died from his injuries within weeks.²⁹² Later that same year, the U.S. FDA announced that it was aware of approximately 385 patients who were exposed to excess radiation (> 0.5 Gy) during CT brain perfusion scans in U.S. hospitals.²⁹³ The exposures were high enough to cause hair loss and redness of the skin in some patients.

²⁸⁶ “Bioscavenger,” PharmAthene Inc., accessed 24 July 2013, <http://www.pharmathene.com/product-portfolio/bioscavenger>; “First Time in Human Study of Protexia,” ClinicalTrials.gov, last modified 16 September 2010, <http://clinicaltrials.gov/ct2/show/NCT00744146>.

²⁸⁷ Melinda E. Wales and Tony E. Reeves, “Organophosphorus Hydrolase as an *in Vivo* Catalytic Nerve Agent Bioscavenger,” *Drug Testing and Analysis* 4, no. 3–4 (2012): 271–281.

²⁸⁸ Manojkumar Valiyaveetil et al., “Crossroads in the Evaluation of Paraoxonase 1 for Protection against Nerve Agent and Organophosphate Toxicity,” *Toxicology Letters* 210, no. 1 (2012): 87–94.

²⁸⁹ Ariel Gore et al., “Efficacy Assessment of Various Anticholinergic Agents against Topical Sarin-Induced Miosis and Visual Impairment in Rats,” *Toxicological Sciences* 126, no. 2 (2012): 515–524.

²⁹⁰ Jean-Marc Collombet, “Nerve Agent Intoxication: Recent Neuropathophysiological Findings and Subsequent Impact on Medical Management Prospects,” *Toxicology and Applied Pharmacology* 255, no. 3 (2011): 229–241.

²⁹¹ Abel J. Gonzalez et al., “Radiological Protection Issues Arising During and after the Fukushima Nuclear Reactor Accident,” *Journal of Radiological Protection* 33, no. 3 (2013): 497–571.

²⁹² Jim Yardley “Indian Man Dies after Radiation Exposure,” *New York Times* (27 April 2010), http://www.nytimes.com/2010/04/28/world/asia/28india.html?_r=0.

²⁹³ “Safety Investigation of CT Brain Perfusion Scans: Update 11/9/2010,” FDA, last modified 22 August 2013, <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm185898.htm>.

For the incidents mentioned above, doses and clinical symptom progressions were unavailable, but such information may be available for hundreds of cases in the System for Evaluation and Archiving of Radiation accidents based on Case Histories (SEARCH) database, a collection of 785 case histories from human cases of radiation exposure.²⁹⁴ With access to the SEARCH database, IDA could use its records to validate or revise the human response models in *AMedP-8(C)*. The database is currently being leveraged by an international group of experts known as the Group to Link nonhuman Primate and Human radiation effects (GLiPH), which is working to combine human and non-human primate response data to improve the medical management of radiation casualties.²⁹⁵

Other sources of radiation effects information that could be useful to the *AMedP-8(C)* effort to model the human response to radiation include dose-response models based on acute radiation accidents in Russia²⁹⁶ and a radiation effects database called FREDERICA, which contains 1,228 radiation exposure records for a variety of flora and fauna, including 269 mammal exposure records.²⁹⁷

2. Medical Countermeasures

Radiation countermeasures can be grouped into three categories based on the timing of their administration.²⁹⁸ Drugs in the first category, administered prior to irradiation, are known as radioprotectants or radioprotectors. Experiments with dozens of candidate radioprotectants have been reported, but amifostine is the only one that is currently approved for use as a radioprotectant.²⁹⁹ Radiation mitigators make up the second class of countermeasures, and they are administered as post-exposure prophylaxis, before the onset of overt symptoms. The final

²⁹⁴ Dieter H. Graessle and Theodor M. Fliedner, “Computer-Assisted Severity of Effect Assessment of Hematopoietic Cell Renewal after Radiation Exposure Based on Mathematical Models,” *Health Physics* 98, no. 2 (2010): 282–289; I. Friesecke et al., “SEARCH: A System for Evaluation and Archiving of Radiation Accidents Based on Case Histories,” *Radiation and Environmental Biophysics* 39, no. 3 (2000): 213–217; B. Maidment et al., *Group to Link Nonhuman Primate and Human Radiation Effects (GLiPH)* (University of Maryland School of Medicine).

²⁹⁵ Maidment et al., *Group to Link Nonhuman Primate and Human Radiation Effects (GLiPH)*.

²⁹⁶ S. V. Osovets et al., “Assessment of Risks and Dose Thresholds for Some Effects of Acute Exposure,” *Health Physics* 100, no. 2 (2011): 176–184; S. V. Osovets et al., “Direct and Indirect Tasks on Assessment of Dose and Time Distributions and Thresholds of Acute Radiation Exposure,” *Health Physics* 102 (2012): 182–195.

²⁹⁷ “FREDERICA Radiation Effects Database” (European Commission, 2013).

²⁹⁸ V. N. Patel et al., “Contemporary Radiation Countermeasures,” *Defence Science Journal* 61, no. 2 (2011): 138–145; Badri N. Pandey et al., “Radiobiological Basis in Management of Accidental Radiation Exposure,” *International Journal of Radiation Biology* 86, no. 8 (2010): 613–635; Deborah Citrin et al., “Radioprotectors and Mitigators of Radiation-Induced Normal Tissue Injury,” *The Oncologist* 15, no. 4 (2010): 360–371.

²⁹⁹ M. I. Koukourakis, “Radiation Damage and Radioprotectants: New Concepts in the Era of Molecular Medicine,” *British Journal of Radiology* 85, no. 1012 (2012): 313–330; “Ethyol (Amifostine) for Injection,” FDA, last modified 14 August 2013, <http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm121181.htm>; David J. Grdina, (*Amifostine: WR2721*) *Diagnostic Radiology Application* (The University of Chicago).

category of radiation countermeasures is therapeutic agents, which are used to treat symptoms of irradiation. Because a number of radiation mitigators are also used as therapeutic agents, all post-exposure radiation countermeasures will be discussed together.

A number of FDA-approved drugs can be used to mitigate the effects of radiation by reducing the amount of internal radiation that the body absorbs. Prussian blue, calcium diethylenetriamine pentaacetate (DTPA), zinc DTPA, and potassium iodide have different mechanisms of action, but all serve to expedite the passing of radioactive materials through the body so they have less time to cause damage.³⁰⁰

Other radiation mitigators include growth factors such as granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF), which stimulate hematopoiesis.³⁰¹ Hematopoiesis can also be induced through the IV administration of mesenchymal stem cells,³⁰² mesenchymal stromal cells,³⁰³ myeloid progenitor cells,³⁰⁴ or hematopoietic stem cells.³⁰⁵ One expert panel concluded that there is strong evidence to support the use of G-CSF or GM-CSF and weak evidence to support hematopoietic stem cell transplantation to treat hematopoietic symptoms of ARS.³⁰⁶ The same expert group also reported recommendations for physiological systems other than the hematopoietic system.³⁰⁷

Although currently there are no approved pharmaceuticals for ARS,³⁰⁸ G-CSF and four other drugs can be used under IND protocol.³⁰⁹ Genistein and 5-androstenediol have both been

³⁰⁰ Joseph F. Weiss and Michael R. Landauer, "History and Development of Radiation-Protective Agents," *International Journal of Radiation Biology* 85, no. 7 (2009): 539–573.

³⁰¹ Patel et al., "Contemporary Radiation Countermeasures"; Pandey et al., "Management of Accidental Radiation Exposure."

³⁰² Sehwan Shim et al., "Mitigating Effects of hUCB-MSCs on the Hematopoietic Syndrome Resulting from Total Body Irradiation," *Experimental Hematology* 41, no. 4 (2013): 346–353 e342; K. X. Hu et al., "The Radiation Protection and Therapy Effects of Mesenchymal Stem Cells in Mice with Acute Radiation Injury," *British Journal of Radiology* 83, no. 985 (2010): 52–58.

³⁰³ Claudia Lange et al., "Radiation Rescue: Mesenchymal Stromal Cells Protect from Lethal Irradiation," *PLoS One* 6, no. 1 (2011): e14486.

³⁰⁴ Vijay K. Singh et al., "Myeloid Progenitors: A Radiation Countermeasure That Is Effective When Initiated Days after Irradiation," *Radiation Research* 177, no. 6 (2012): 781–791.

³⁰⁵ Shigetaka Asano, "Current Status of Hematopoietic Stem Cell Transplantation for Acute Radiation Syndromes," *International Journal of Hematology* 95, no. 3 (2012): 227–231.

³⁰⁶ Nicholas Dainiak et al., "First Global Consensus for Evidence-Based Management of the Hematopoietic Syndrome Resulting from Exposure to Ionizing Radiation," *Disaster Medicine and Public Health Preparedness* 5, no. 3 (2011): 202–212.

³⁰⁷ Nicholas Dainiak et al., "Literature Review and Global Consensus on Management of Acute Radiation Syndrome Affecting Nonhematopoietic Organ Systems," *Disaster Medicine and Public Health Preparedness* 5, no. 3 (2011): 183–201.

³⁰⁸ Mang Xiao and Mark H. Whitnall, "Pharmacological Countermeasures for the Acute Radiation Syndrome," *Current Molecular Pharmacology* 2, no. 1 (2009): 122–133.

³⁰⁹ V. K. Singh et al., "A Review of Radiation Countermeasure Work Ongoing at the Armed Forces Radiobiology Research Institute," *International Journal of Radiation Biology* 88, no. 4 (2012): 296–310.

shown to be efficacious in mice.³¹⁰ CBLB502 has also been tested in mouse and non-human primate models and shown efficacy in pre-exposure and post-exposure uses.³¹¹ In addition to being safe and effective as a radioprotectant in a mouse model (with a dose reduction factor of 1.16)³¹² and when administered after exposure,³¹³ Ex-Rad (ON01201.Na) has also undergone preclinical safety experiments in other animal species including rats, rabbits, canines, and non-human primates.³¹⁴

3. Animal Models

As for chemical and biological countermeasures, approval for radiation countermeasures must sometimes rely on animal models, since human efficacy testing is unethical. A number of models that represent various sub-syndromes of ARS in humans have recently been developed in different animal species. Mouse and non-human primate models have been developed for gastrointestinal symptoms of ARS.³¹⁵ Additionally, the hematopoietic sub-syndrome has been modeled in mice, minipigs, and non-human primates.³¹⁶ Lastly, mice, rats, canines, pigs, and

³¹⁰ Vijay K. Singh et al., “Effects of Genistein Administration on Cytokine Induction in Whole-Body Gamma Irradiated Mice,” *International Immunopharmacology* 9, no. 12 (2009): 1401–1410; V. K. Singh et al., “Administration of 5-Androstenediol to Mice: Pharmacokinetics and Cytokine Gene Expression,” *Experimental and Molecular Pathology* 84, no. 2 (2008): 178–188.

³¹¹ L. G. Burdelya et al., “An Agonist of Toll-Like Receptor 5 Has Radioprotective Activity in Mouse and Primate Models,” *Science* 320, no. 5873 (2008): 226–230; V. I. Krivokrysenko et al., “Identification of Granulocyte Colony-Stimulating Factor and Interleukin-6 as Candidate Biomarkers of CBLB502 Efficacy as a Medical Radiation Countermeasure,” *Journal of Pharmacology and Experimental Therapeutics* 343, no. 2 (2012): 497–508.

³¹² Anthony D. Kang et al., “ON01210.Na (Ex-RAD®) Mitigates Radiation Damage through Activation of the AKT Pathway,” *PLoS One* 8, no. 3 (2013): e58355; Sanchita P. Ghosh et al., “Amelioration of Radiation-Induced Hematopoietic and Gastrointestinal Damage by Ex-RAD® in Mice,” *Journal of Radiation Research* 53, no. 4 (2012): 526–536; Sanchita P. Ghosh et al., “Radiation Protection by a New Chemical Entity, Ex-Rad: Efficacy and Mechanisms,” *Radiation Research* 171, no. 2 (2009): 173–179.

³¹³ Shubhankar Suman et al., “Administration of ON 01201.Na after Exposure to Ionizing Radiation Protects Bone Marrow Cells by Attenuating DNA Damage Response,” *Radiation Oncology* 7, no. 6 (2012).

³¹⁴ Amy W. Chun et al., “Effects of Formulation and Route of Administration on the Systemic Availability of Ex-RAD®, a New Radioprotectant, in Preclinical Species,” *Biopharmaceutics & Drug Disposition* 32, no. 2 (2011): 99–111.

³¹⁵ Thomas J. MacVittie et al., “The Acute Gastrointestinal Subsyndrome of the Acute Radiation Syndrome: A Rhesus Macaque Model,” *Health Physics* 103, no. 4 (2012): 411–426; T. J. MacVittie et al., “The Prolonged Gastrointestinal Syndrome in Rhesus Macaques: The Relationship between Gastrointestinal, Hematopoietic, and Delayed Multi-Organ Sequelae Following Acute, Potentially Lethal, Partial-Body Irradiation,” *Health Physics* 103, no. 4 (2012): 427–453; Catherine Booth et al., “Acute Gastrointestinal Syndrome in High-Dose Irradiated Mice,” *Health Physics* 103, no. 4 (2012): 383–399; Catherine Booth et al., “Evidence of Delayed Gastrointestinal Syndrome in High-Dose Irradiated Mice,” *Health Physics* 103, no. 4 (2012): 400–410; M. Moroni et al., “Hematopoietic Radiation Syndrome in the Gottingen Minipig,” *Radiation Research* 176, no. 1 (2011): 89–101; Maria Moroni et al., “Hematological Changes as Prognostic Indicators of Survival: Similarities between Gottingen Minipigs, Humans, and Other Large Animal Models,” *PLoS One* 6, no. 9 (2011): e25210.

³¹⁶ Ann M. Farese et al., “A Nonhuman Primate Model of the Hematopoietic Acute Radiation Syndrome Plus Medical Management,” *Health Physics* 103, no. 4 (2012): 367–382; T. J. MacVittie et al., “The Prolonged Gastrointestinal Syndrome in Rhesus Macaques: The Relationship between Gastrointestinal, Hematopoietic,

non-human primates are all being developed as animal models for radiation-induced lung injuries.³¹⁷

and Delayed Multi-Organ Sequelae Following Acute, Potentially Lethal, Partial-Body Irradiation,” *Health Physics* 103, no. 4 (2012): 427–453; P. Artur Plett et al., “Establishing a Murine Model of the Hematopoietic Syndrome of the Acute Radiation Syndrome,” *Health Physics* 103, no. 4 (2012): 343–355; Moroni et al., “Hematopoietic Radiation Syndrome in the Gottingen Minipig”; M. Moroni et al., “The Gottingen Minipig Is a Model of the Hematopoietic Acute Radiation Syndrome: G-Colony Stimulating Factor Stimulates Hematopoiesis and Enhances Survival from Lethal Total-Body Gamma-Irradiation,” *International Journal of Radiation Oncology Biology Physics* 86, no. 5 (2013): 986–992.

³¹⁷ Jacqueline P. Williams et al., “Animal Models and Medical Countermeasures Development for Radiation-Induced Lung Damage: Report from an NIAID Workshop,” *Radiation Research* 177, no. 5 (2012): e0025–0039; Isabel L. Jackson et al., “A Preclinical Rodent Model of Radiation-Induced Lung Injury for Medical Countermeasure Screening in Accordance with the FDA Animal Rule,” *Health Physics* 103, no. 4 (2012): 463–473.

3. Estimation of Effort Required to Extend *AMedP-8* Methodology

A. Introduction

The literature review revealed three categories of work that could be carried out to update or extend the *AMedP-8(C)* methodology: (1) editorial changes to the text of future versions of *AMedP-8* or related documents, (2) the incorporation of new data into existing *AMedP-8(C)* models, and (3) the comparison of *AMedP-8(C)* models to other published models or databases for validation or revision. Estimates for the level of effort required to complete future analyses identified in this review were based on IDA's prior experiences performing analyses in this field.

B. Editorial Changes

Some recent advances, such as the truncated primary dosing schedule for the anthrax vaccine BioThrax, represent important changes to the application of the medical management of CBRN casualties, but cause little modification to the *AMedP-8(C)* methodology. Other similar developments include the approval of another antibiotic, Levaquin (levofloxacin), as a plague post-exposure prophylaxis and treatment and the inclusion of Imvamune smallpox vaccines for individuals contraindicated for the ACAM2000 vaccine. Advances such as these may require some editorial revisions to outdated information in text or tables but will not require significant analysis by IDA researchers.

Incorporating changes of this kind into future versions of *AMedP-8* or other related documents represents a relatively minor level of effort for IDA researchers. If done in isolation, this work would take an estimated one person-month of effort to rewrite, review, and publish. However, it is likely that these changes would be made as part of a larger effort to revamp the methodology (i.e., development of the next version of *AMedP-8*), and these changes would add an insubstantial amount of work to that effort.

C. Incorporation of New Data into Existing Models

The second category of changes involves incorporating known sets of data into the *AMedP-8(C)* methodology. As described in the sections above, animal and human response data have become available for a number of agents modeled in *AMedP-8(C)*. In particular, potential changes were identified for a number of biological agent submodels: anthrax infectivity and lethality; botulism infectivity, lethality, and duration of illness; brucellosis infectivity; glanders infectivity; plague infectivity and lethality; Q fever duration of illness; smallpox infectivity

(modified by potential post-exposure prophylactic administration of VIG); and tularemia duration of illness.

The process of extracting the latest data from published sources, fitting a distribution to the new combined data set, and documenting the results is estimated to take, on average, one-quarter person-month of effort per submodel. As there are 12 submodels that could change, this effort is estimated to take a total of approximately three person-months. Before any changes are made to the human response models in *AMedP-8(C)*, a higher-level analysis should be conducted to determine whether new data would significantly impact the casualty estimates and improve utility for military planners. Such an analysis is estimated to require approximately one person-month.

In addition to the data related to the biological agents in *AMedP-8(C)*, significant information is available on the medical countermeasures available to prevent, mitigate, or treat the effects of radiation exposure. The impact of radioprotectant drugs and radiation injury treatments on the casualty estimate should be a focus of future IDA analysis. A few publications that provided concrete efficacy data on the various countermeasures were gathered in this literature review, but more significant work is required to quantify their effects. For this reason, this analysis is estimated to require three person-months of effort.

A worthwhile related effort is a validation of the *AMedP-8(C)* radiation models using case histories from the SEARCH radiation effects database. A first step for IDA would be to gain access to the 785 case histories in the database. Although it is unlikely that all cases report estimated doses, it is possible that many cases can be used to revise or validate the *AMedP-8(C)* radiation models. This effort is estimated to require four person-months of effort.

IDA should also maintain an awareness of ongoing GLiPH efforts to combine human and non-human primate radiation response data, which leverages the SEARCH database. IDA should evaluate any pertinent work performed by the GLiPH team for possible incorporation into the *AMedP-8(C)* methodology, although the level of effort required to do so is impossible to estimate without a better understanding of the GLiPH team's work.

D. Evaluation of Alternative Models

The third category of changes that could be made to the *AMedP-8(C)* methodology involves a higher-level assessment of the process and an evaluation of whether the human response models in *AMedP-8(C)* are the best models to use in light of recently published alternatives. Alternative dose-response models were identified for anthrax and radiation. In addition, a general dose-response method of pooling data from multiple species was described for both brucellosis and Q fever.³¹⁸ This method, if appropriate, could be extended to combine data from multiple

³¹⁸ Teske et al., "Dose-Response Models for *Brucella* Species," Sushil B. Tamrakar et al., "Dose-Response Model of *Coxiella burnetii* (Q Fever)," *Risk Analysis* 31, no. 1 (Jan 2011): 120–128.

species for every agent modeled in *AMedP-8(C)* and would potentially replace the hierarchy of data quality used throughout the *AMedP-8(C)* methodology.

Understanding and evaluating the utility of alternative methodologies is a significant effort that is estimated to require three person-months of effort. The level of effort for any potential follow-on work to revise the *AMedP-8(C)* methodology to incorporate new models deemed more appropriate would have to be estimated at a later time.

4. Recommended Future Analyses

Based on IDA's understanding of the available literature and the needs of the sponsor, the IDA research team recommends a number of future efforts related to *AMedP-8(C)* human response modeling. These include addressing editorial changes and past methodological advances (1), considering new data (2, 3, and 4), evaluating alternative models (5), and investigating outstanding topics recommended in prior annual reviews (6 and 7).

1. As a NATO document, *AMedP-8(C)* is subject to a periodic review every three years. Since its 2011 publication, the *AMedP-8(C)* methodology has been expanded to include human response parameters for additional agents and the consideration of medical care. Given these significant advancements, IDA recommends that a new version of *AMedP-8* be proposed at the 2014 review. The proposal should include incorporating, at a minimum, the new agents, the impact of medical care, and any editorial changes to keep the content current, as described in the previous section of this document.
2. During this review, the IDA team was successful in identifying new sources of data relevant to updating the *AMedP-8(C)* methodology. In particular, data are available that could impact the anthrax, botulism, brucellosis, glanders, plague, Q fever, smallpox, and tularemia models. In addition, IDA continues to pursue access to the human response studies conducted through the MRV program in the 1950s and 1960s, which could provide data useful to the Q fever, SEB, and tularemia models. IDA should conduct cost-benefit analyses to determine whether the new data would significantly improve the military medical planning process and warrant changes to the *AMedP-8(C)* methodology.
3. The IDA team should quantify the impact on the casualty estimate of radioprotectant drugs, radiation mitigators, and radiation therapeutic agents in NATO member national inventories or those in procurement, but not fielded. As some of these countermeasures are FDA-approved or have emergency use IND status, some efficacy data must be available.
4. Case histories from the SEARCH radiation effects database should be reviewed to assess their value in validating or revising the *AMedP-8(C)* radiological agent human response models. In addition to requesting access to the SEARCH database, IDA should reach out to and collaborate with the GLiPH team, which is leveraging the SEARCH data to establish correlations between human and non-human primate radiation exposures. With a better understanding of the GLiPH team's efforts, IDA can determine how their work might fit within the framework of the *AMedP-8(C)* methodology.

5. The IDA team should compare the *AMedP-8(C)* dose-response models to the alternative dose-response models discovered in this literature review and any other published models. In particular, alternative dose-response models specific to anthrax and radiation were discovered, as well as a more general method of pooling infectivity data from multiple species. Analyses should be conducted to compare each alternative methodology with the existing models within *AMedP-8(C)*. The result of these analyses should be a recommendation to continue with the current methodology or to change it, along with an estimate of the level of effort required to do so.
6. Many chemical and biological agents of interest to various government agencies are candidates for future inclusion in *AMedP-8(C)*. Levels of effort to incorporate more than 40 agents into the *AMedP-8(C)* methodology were estimated in the 2009 review, yet only a small fraction has been modeled. IDA should develop a prioritization scheme for future inclusion of the remaining agents in *AMedP-8(C)* based on an analysis of the military threat or capability to NATO nations and the availability of modeling data for each agent.
7. As discussed in prior annual reviews, IDA stands ready to investigate the feasibility of incorporating the estimation of psychological casualties into the *AMedP-8(C)* methodology if and when this becomes a sponsor priority.

Appendix A

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Appendix B

Abbreviations

AIG	Anthrax Immune Globulin
<i>AMedP-8</i>	<i>Allied Medical Publication 8</i>
<i>AMedP-8(C)</i>	<i>Allied Medical Publication 8 (C)</i>
APSV	Aventis Pasteur Smallpox Vaccine
ARS	Acute Radiation Syndrome
CBRN	Chemical, Biological, Radiological, and Nuclear
CDC	Centers for Disease Control and Prevention
CFU	Colony Forming Unit
CUD	Common User Database
DAM	Diacetylmonoxime
DNA	Deoxyribonucleic Acid
DOD	Department of Defense
DTPA	Diethylenetriamene Pentaacetate
dVVL	Defective Vaccinia Virus Lister
EEE	Eastern Equine Encephalitis
EF	Edema Factor
FDA	Food and Drug Administration
G-CSF	Granulocyte-Colony Stimulating Factor
GB	Sarin
GLiPH	Group to Link Nonhuman Primate and Human Radiation Effects
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
HD	Distilled Mustard
IDA	Institute for Defense Analyses
IM	Intramuscular
IND	Investigational New Drug
ISID	International Society for Infectious Diseases
IV	Intravenous
KBMA	Killed But Metabolically Active
LC ₅₀	Median Lethal Concentration
LD ₅₀	Median Lethal Dose
LF	Lethal Factor
LRRi	Lovelace Respiratory Research Institute
LVS	Live Vaccine Strain
MINA	Monoisonitrosoacetone
MIPLD	Mouse Intraperitoneal Lethal Dose
MIPLD ₅₀	Median Mouse Intraperitoneal Lethal Dose
<i>MMWR</i>	<i>Morbidity and Mortality Weekly Report</i>

MRV	Military Research Volunteer
MVA	Modified Vaccinia Ankara
MyD88	Myeloid Differentiation Protein 88
NATO	North Atlantic Treaty Organization
OPH	Organophosphorus Hydrolase
OTSG	U.S. Army Office of the Surgeon General
PA	Protective Antigen
PARP	Poly ADP Ribose Polymerase
PGA	Poly-Gamma-D-Glutamic Acid
PIV	Pseudoinfectious Virus
QFS	Q Fever Fatigue Syndrome
rPA	Recombinant Protective Antigen
SEARCH	System for Evaluation and Archiving of Radiation Accidents Based on Case Histories
SEB	Staphylococcal Enterotoxin B
SNS	Strategic National Stockpile
UK	United Kingdom
U.S.	United States
USAMRIID	United States Army Medical Research Institute of Infectious Diseases
VEE	Venezuelan Equine Encephalitis
VIG	Vaccinia Immune Globulin
VX	Methylphosphonothioic Acid Nerve Agent
WEE	Western Equine Encephalitis
WWII	World War Two

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