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INSTITUTE FOR DEFENSE ANALYSES

Parameters for Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia

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Executive Summary

As part of its broader casualty estimation methodology, Allied Medical Publication 8 (AMedP-8(C)), *NATO Planning Guide for the Estimation of CBRN Casualties*,[1] defines a framework for modeling the human response to biological agent exposure and incorporates the specific parameters necessary to model two contagious diseases (pneumonic plague and smallpox) and three non-contagious diseases (anthrax, botulism, and Venezuelan equine encephalitis (VEE)).

This document describes the extension of the *AMedP-8(C)* biological human response model to five additional non-contagious agents: brucellosis, glanders, Q fever, staphylococcal enterotoxin B (SEB), and tularemia. It includes proposed modeling parameter values for each agent, together with the derivation of those values. The document further details the analytical choices made when determining parameters in order to support transparency and reproducibility of results.

Approach

Following the *AMedP-8(C)* methodology, this document describes parameters and associated values used to populate its various submodels, for each agent. These submodels are:

- Infectivity/Effectivity. A model of the number of exposed individuals who become ill as a function of their inhaled dose.
- Lethality. The estimated number of exposed individuals who become fatalities in the absence of treatment.
- Incubation/Latent Period. The duration of time between exposure and the onset of signs and symptoms.
- Illness Profile. A description of severity of illness over time, based on a severity scale and definitions defined in *AMedP-8(C)*.
- Duration of Illness. The time between onset of signs and symptoms and death or recovery.

[1] North Atlantic Treaty Organization (NATO), *AMedP-8(C): NATO Planning Guide for the Estimation of CBRN Casualties, Ratification Draft 1*, DRAFT, February 2010.

In addition, this document makes note of the availability and efficacy of prophylactic medical countermeasures. In the *AMedP-8(C)* methodology, prophylaxis is treated as a factor modifying infectivity/effectivity. While not explicitly considered in the derivation of infectivity/effectivity parameters and values for any of the five agents considered in this document, the information is provided for the record.

Summary of Proposed Parameter Values

The values proposed for each of these submodels were derived from extensive reviews of published literature. When raw data were available, they were used directly to define original parameters or to independently verify values calculated elsewhere. When data were limited, issues and gaps were identified and a strategy developed to generate the best possible parameter values given the constraints. This document describes in detail the available data, identified issues and gaps, and the analyses conducted in the course of populating the submodels.

Controlled human exposure data exist for some of the agents considered in this document. These data were obtained from vaccine trials and other experiments but were never published in complete form. Analyses of these data were included in various source documents, but either could not be reproduced by the authors or could only be reproduced in part. This leads to some inconsistencies between this study and previous analyses. It is the recommendation of the authors to use the parameters described, but that the complete controlled human exposure data be collated and published to allow for a thorough analysis to derive the human response parameters of interest. Once that is complete, it may be of value to then pursue a research program to further quantitatively characterize the infectivity, lethality, incubation, duration and course of illness of these biological agents.

The parameter values proposed for each submodel, by agent, are summarized in the sections that follow. The derivation of the proposed distributions, parameters, and values are provided in the body of this document.

Brucellosis

Brucellosis Model Parameters Summary Table

Submodel	Type	Parameters
Infectivity	Lognormal distribution	ID_{50} = 949 organisms, Probit slope = 2.58 probits/log(dose)
Lethality	Case fatality rate	0%
Incubation period	Weibull distribution	$\alpha = 1.72$, $\beta = 10.2$
Duration of illness		
• Total	Gamma distribution	$k = 3.97$, $\theta = 2.54$
• Abrupt onset Stage 1	Same as total	
• Insidious onset Stage 1	Gamma distribution	$k = 0.827$, $\theta = 5.32$
• Insidious onset Stage 2	Total minus Stage 1	

Brucellosis Abrupt Onset Illness Profile

	Stage 1
Signs and Symptoms (S/S)	Fever, sweats, chills, headache, malaise, fatigue, arthralgia, myalgia, anorexia, weight loss
S/S Severity	3 (Severe)
Outlook	Individual will likely recover from illness

Brucellosis Insidious Onset Illness Profile

	Stage 1	Stage 2
Signs and Symptoms (S/S)	Fever, malaise	Fever, sweats, chills, headache, malaise, fatigue, arthralgia, myalgia, anorexia, weight loss
S/S Severity	1 (Mild)	3 (Severe)
Outlook	Individual will progress to Stage 2	Individual will likely recover from illness

Glanders

Glanders Model Parameters Summary Table

Submodel	Type	Parameters
Infectivity	Lognormal distribution	ID_{50} = 24.5 CFU Probit slope = 1.93 probits/log(dose)
Lethality	Case fatality rate	70%
Incubation period	Lognormal distribution	Mean = 8.29 days Standard deviation = 13.0 days
Duration of illness	Weibull function	$\alpha = 1.90$, $\beta = 26.0$
Stage 1	Rate	30% of total duration
Stage 2	Rate	45% of total duration
Stage 3	Rate	25% of total duration

Illness Profile for Glanders

	Stage 1	Stage 2	Stage 3	Stage 4 (survivors)	Stage 4 (non-survivors)
Signs and Symptoms (S/S)	Localized pain and inflammation, fever, swelling, chills, and phlegmon	Cough, suppuration, red streaks, papular eruption nasal discharge, abscess, pain, and ulcerations	Diarrhea, emaciation, pustules, necrosis, dyspnea, and delirium	Chronic glanders	None (Dead)
S/S Severity	Severity Level 1 (“Mild”)	Severity Level 2 (“Moderate”)	Severity Level 3 (“Severe”)	Severity Level 2 (“Moderate”)	
Outlook	Individual will progress to Stage 2	Individual will progress to Stage 3	Individual will progress to Stage 4	Individual will likely recover after a prolonged illness	Death

Q Fever

Q Fever Model Parameters Summary Table

Submodel	Type	Parameters
Infectivity	Lognormal distribution	ID_{50} = 30 organisms; Probit slope = 0.782 probits/log(dose)
Lethality	Rate	0%
Incubation period	Log-linear function	α = 19.6, β = -1.88
Duration of illness	Lognormal distribution	μ = 2.4, σ = 0.51

Q Fever Illness Profile

	Stage 1
Signs and Symptoms (S/S)	Fever, chills, headache, myalgia. Pneumonia; hepatitis.
S/S Severity	2 (Moderate)
Outlook	Patient is likely to recover

SEB

Inhalational SEB Intoxication Model Parameters Summary Table

Submodel	Type	Parameters
Infectivity	Lognormal distribution	ED_{50} = 0.026 μg; Probit slope = 2.54 probits/log(dose)
Lethality	Lognormal distribution	LD_{50} = 1.66 μg; Probit slope = 3.00 probits/log(dose)
Incubation period	Constant	9 hours
Duration of illness		
Stage 1	Log-linear function	a = 6.10, b = 371 Maximum = 192 hours
Stage 2	Constant	One week

Illness Profile for Inhalational SEB Intoxication

	Stage 1	Stage 2 (survivors)	Stage 2 (non-survivors)
Signs and Symptoms (S/S)	Cough, headache, chest pain, myalgia, elevated temperature, vomiting, nausea, and anorexia	Non-productive cough	None (Dead)
S/S Severity	Severity Level 3 (“Severe”)	Severity Level 1 (“Mild”)	
Outlook	Individual will progress to Stage 2	Individual will likely recover	Death

Tularemia

Pneumonic Tularemia Model Parameters Summary Table

Submodel	Type	Parameters
Infectivity	Lognormal distribution	ID_{50} = 10 organisms Probit slope = 1.90 probits/log(dose)
Lethality	Rate	75%
Incubation period	For doses <10^5 organisms:	
	Log-linear function	α = 6.54, β = -0.821
	For doses 10^5 to 10^7 organisms:	
	Log-quadratic function	α_0 = 11.0; α_1 = -2.59; α_1 = 0.176
	For doses > 10^7 organisms:	
	Constant	1.5 days
Duration of illness (non-survivor)		
Stage 1	Constant	9 days
Stage 2	Constant	6 days
Duration of illness (survivor)		
Stage 1	Constant	12 days
Stage 2	Constant	28 days
Stage 3	Constant	12 weeks

Illness Profile for Pneumonic Tularemia

	Stage 1 (all)	Stage 2 (non-survivors)	Stage 2 (survivors)	Stage 3 (survivors)
Signs and Symptoms (S/S)	High fever, headache, chills, sore throat, myalgia, chest pain	Stage 1 S/S plus severe pneumonia, respiratory distress	Stage 1 S/S plus mild pneumonia	Malaise, severe weakness
S/S Severity	Severity Level 3 (“Severe”)	Severity Level 4 (“Very Severe”)	Severity Level 3 (“Severe”)	Severity Level 2 (“Moderate”)
Outlook	Individual will progress to Stage 2	Death	Individual will progress to Stage 3	Recovery

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1. Introduction

In February 2010, the North Atlantic Treaty Organization (NATO) distributed to member nations the first ratification draft of a revised planning methodology for estimating casualties resulting from chemical, biological, radiological, or nuclear (CBRN) attacks on military populations. That document, *Allied Medical Publication 8 (AMedP-8(C): NATO Planning Guide for the Estimation of CBRN Casualties*,[1] defines a framework for modeling the human response to biological agent exposure and incorporates the specific parameters necessary to model two contagious diseases (pneumonic plague and smallpox) and three non-contagious diseases (anthrax, botulism, and Venezuelan equine encephalitis (VEE)).

AMedP-8(C) models the human response to biological agent exposure using five submodels: infectivity/effectivity, lethality, incubation/latent period, illness profile, and duration of illness. Using the *AMedP-8(C)* methodology, the human response to five additional biological agents was modeled. This document summarizes the five submodel approach depicted in *AMedP-8(C)* and describes the parameters needed to model brucellosis, glanders, Q fever, staphylococcal enterotoxin B (SEB), and tularemia. It further details the analytical choices made when determining parameters in order to support transparency and reproducibility of results.

The goal of this effort was two-fold: 1) populate the submodel parameters for each of the five new agents and 2) document the derivation of these parameters. The following section describes the submodels and the type of information needed to model the human response to biological agents. The subsequent section in this chapter details the IDA study team's approach to finding that information and data selection criteria. Each of the remaining chapters reports the results of the literature search for one of the five agents and specifies the parameters chosen for each submodel.

A. Five Submodel Approach

The five submodels described in this section form the framework of the *AMedP-8(C)* biological agent methodology. Before the agent-specific parameters can be understood, a general knowledge is required of how the submodels fit together and how

[1] North Atlantic Treaty Organization (NATO), *AMedP-8(C): NATO Planning Guide for the Estimation of CBRN Casualties, Ratification Draft 1*, DRAFT, February 2010.

each is characterized. This section will provide a basis for that understanding and allow the reader to more fully comprehend the meaning of the parameters in the following chapters.

The human response portion of the casualty estimation methodology, which the five submodels comprise, requires only one type of input: the dose of inhaled agent associated with each individual (or each group of individuals receiving the same dose). Using this value, the five submodels are employed as shown in Figure 1 to determine the number of individuals expected to become ill, the number of individuals expected to die, the time between exposure and the onset of signs and symptoms of illness, the severity of these signs and symptoms over time, and finally the time at which the signs and symptoms change and death or recovery occurs. For a complete understanding of how the five submodels are combined to produce a casualty estimate, the reader is directed to a previously published description of the *AMedP-8(C)* biological agent methodology.[2] The submodel descriptions from this reference document are repeated below to clarify the type of information sought in the literature search for the new agents.

[2] Lucas A. LaViolet and Carl A. Curling, *A New Methodology for Estimating Non-Contagious Biological Agent Casualties as a Function of Time*, IDA Non Standard Document D-4062 (Alexandria, VA: Institute for Defense Analyses, June 2010).

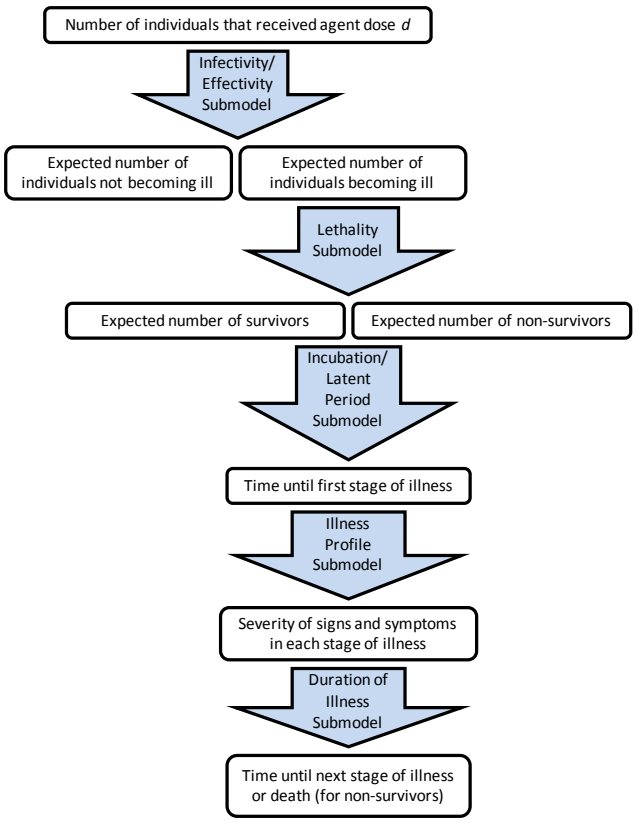

Figure 1. Biological Agent Human Response Submodel Overview

1. Infectivity/Effectivity

The first human response submodel, called the infectivity submodel for replicating organisms (viruses, bacteria, rickettsiae) and the effectivity submodel for biotoxins, is used to estimate the number of individuals that become ill as a function of their inhaled doses. This portion of the human response methodology defines the likelihood of an exposed individual becoming both infected/effected and ill. Individuals who are sub-clinically infected/effected, but who never exhibit signs and symptoms of illness, will not present to the medical system and are excluded from the casualty count. Depending on the available data, the infectivity/effectivity submodel may be characterized as a dose-dependent probability distribution or as a threshold dose at or above which all (and below which no) individuals become ill.

If vaccines or antibiotics are efficacious in protecting against a particular biological agent, such medical countermeasures are incorporated into the infectivity/effectivity submodel. The rate of protection is represented as the efficacy of the prophylaxis when administered prior to the onset of signs and symptoms and is modeled as a multiplier that reduces the size of the vulnerable population. For example, if a vaccine was judged to be 95% efficacious in preventing illness, then the infectivity/effectivity calculation would

only be applied to 5% of the vaccinated, exposed individuals; the rest of the exposed individuals would be fully protected.

2. Lethality

The lethality submodel yields the estimated number of exposed individuals that become fatalities in the absence of treatment and is designed to be flexible enough to account for the different ways the probability of death is defined in the literature. Most lethality experiments result in an unconditional probability of lethality, the sample probability of death given (or dependent only on) exposure, which is often a function of dose. In contrast, case fatality rates report the conditional probability of death given illness, or the sample fraction of ill individuals that die. Both of these forms of expressing lethality following biological agent exposure are acceptable, and the available data should inform the decision of which to choose. Which representation is chosen will then dictate the method of implementation to determine the number of individuals expected to die.

To avoid the case where the expected number of fatalities exceeds the expected number of ill individuals, the unconditional probability of lethality must be less than or equal to the probability of infectivity/effectivity for all doses. On the other hand, the conditional probability of death given illness is not constrained by the probability of infectivity/effectivity and may range from 0 to 100%.

For simplicity of the model, a fatality rate of 1% or below will be considered negligible and a fatality rate of 0% will be assumed. Similarly, in the absence of a well-quantified fatality rate, 100% lethality may be assumed based on qualitative descriptions such as “highly lethal without treatment” or “nearly always fatal.”

3. Incubation/Latent Period

Biological agents often cause diseases that manifest signs and symptoms as late as many days after exposure. The duration of time between exposure and the onset of signs and symptoms is known as the incubation period (or latent period for toxins). The incubation/latent period submodel is used to determine the number of individuals progressing through this asymptomatic period and entering the first stage of illness (at which time signs and symptoms initially manifest) on each day.

This submodel is characterized by the probability of becoming symptomatic as a function of time, which may be represented as a continuous probability distribution that is either dose-dependent or independent of dose.

4. Illness Profile

The illness profile submodel translates the qualitative aspects of a disease (the severity of illness over time) into a quantitative representation useful for estimating

casualties. Derived from clinical descriptions of a disease, the illness profile is characterized by one or more illness stages, each with a unique combination of signs and symptoms correlated to an illness severity level.

In practice, the signs and symptoms of a disease over time dictate the number of stages in the illness profile. For instance, if the typical course of a particular disease progressed from one sign and symptom complex to a markedly different combination of signs and symptoms to complete recovery, then the illness profile would reflect this by dividing the disease into two stages, one categorized by the first set of signs and symptoms, and one by the second set.

The illness severity level scale shown in Table 1 is then used to rate the signs and symptoms in each stage of illness. As the *AMedP-8(C)* methodology is dual purposed to aid in medical and operational planning, the five illness severity levels address both the individual's medical condition and his operational effectiveness.

Table 1. Illness Severity Levels—Definitions

Severity	Degree	Description
0	No Observable Effect	Although some exposure to an agent or effect may have occurred, no observable illness (as would be indicated by manifested signs and symptoms) has developed
1	Mild	Illness manifesting signs and symptoms of such severity that individuals can care for themselves or be helped by untrained personnel; condition may not impact ability to conduct the assigned mission
2	Moderate	Illness manifesting signs and symptoms of such severity that medical care may be required; general condition permits treatment as outpatient and some continuing care and relief of pain may be required before definitive care is given; condition may be expected to interrupt or preclude ability to conduct the assigned mission
3	Severe	Illness manifesting signs and symptoms of such severity that there is cause for immediate concern but there is no imminent danger to life; individual is acutely ill and likely requires hospital care. Indicators are questionable – condition may or may not reverse without medical intervention; individual is unable to conduct the assigned mission due to severity of illness
4	Very Severe	Illness manifesting signs and symptoms of such severity that life is imminently endangered. Indicators are unfavorable – condition may or may not reverse even with medical intervention; prognosis is death without medical intervention; individual is unable to conduct the assigned mission and is unexpected to return to the mission due to severity of illness

5. Duration of Illness

Outputs from the duration of illness submodel include the numbers of individuals expected to enter each stage of illness (other than the first) for each day and the daily number of individuals expected to die. At a minimum, the duration of illness is characterized by an estimate of the total time between sign and symptom onset and either death or the cessation of signs and symptoms. To capture some of the variability in the duration of illness, a continuous probability distribution defining the probability of completing the disease as a function of time may be used to represent the total symptomatic period. If additional data are available to characterize the duration of time spent in each stage of illness, and the times spent in each stage of illness are assumed to be independent variables, then it is possible to model each stage of illness using a separate probability distribution. If no data exist to support modeling each stage of illness on its own, one probability distribution may describe the total duration of illness, and individuals may be assumed to spend an equal (or some other proportional) amount of time in each of the stages.

B. Research Approach

The usefulness of the submodel parameter values presented in the subsequent chapters of this document depends heavily on both the availability of pertinent data sources and the quality of the data found therein. When raw data were available, they were used directly to define original parameters or to independently verify values calculated elsewhere. When data were limited, issues and gaps were identified and a strategy developed to generate the best possible parameter values given the constraints. This section outlines the methodological approach chosen to manage the varying levels of data availability and quality and to ultimately populate the five submodels for each of the five agents. The first part of this section describes a variety of data sources and ranks each source type according to its likelihood to lead to useful submodel parameters. The second part presents in detail the literature search and review process for finding and evaluating these data sources.

1. Hierarchy of Source Data

In the search for data for each of the agents, a wide range of sources was reviewed. For certain agents, data exist from controlled human experiments conducted specifically to better understand the human response to exposure. Such data are ideal because the exact parameters required for modeling human response, including both inhaled dose and the resulting effects, are often captured, allowing for dose-dependent human response models.

On the other hand, it is rare to encounter a record of a naturally occurring outbreak or accidental laboratory exposure for which the dose of agent inhaled is known precisely.

Nonetheless, these accounts sometimes provide useful descriptions of the disease and may also inform the incubation/latent period and duration of illness submodels.

In the absence of useful human data, controlled animal studies are typically the best sources for deriving submodel parameters. Due to their genetic similarity to humans, primate species are generally viewed as the best models for human response effects, followed by non-primate mammals, and finally non-mammalian species. Yet, even documented animal experimental results are sometimes difficult to find or may not supply the needed submodel parameter values. In this case, parameters may be derived from in vitro studies, expert opinion, or extrapolation from similar agents; as a last resort, parameters may simply be estimated. Table 2 provides a summary list of the various types of data sources considered, ordered by the expected relevance of the source data to developing submodel parameters.

Table 2. Biological Agent Literature Review Data Source Preferences

Data Source	Relevance of Data
Controlled Human Experiments	Highest
Human Outbreak Data	↓
Accidental Laboratory Exposures	↓
Controlled Animal Studies	↓
Primates	↓
Non-Primate Mammals	↓
Non-Mammals	↓
In Vitro Studies	↓
Expert Opinion	↓
Extrapolation from Similar Agents	↓
Best Guesses	Lowest

2. Literature Search and Review

At the onset of the search for parameter values, a few particularly relevant references, including comprehensive reviews of the present knowledge of biological agents and documentation from previous modeling efforts, were identified as “capstone” documents. This section briefly describes each of the four “capstone” documents and then explains their role in the development of submodel parameters for the five new agents.

The document most directly applicable to modeling human response is the *Biological Agent Exposure and Casualty Estimation: AMedP-8 (Biological) Methods*

Report.[3] This report, as stated on its second page, "describes the background and methods used to generate data and tables for Allied Medical Publication 8 (AMedP-8), the Medical Planning Guide for the Estimation of NBC Battle Casualties, Volume II (Biological)."[4] In essence, it is a summary of the work conducted to develop the previous version of the AMedP-8 biological agent methodology upon which the *AMedP-8(C)* methodology is built. The same types of information are needed for both versions of the human response methodology, making the *AMedP-8 (Biological) Methods Report* an invaluable resource.

Table 3. Capstone Documents Used in the Development of New Agent Models

	Brucellosis	Glanders	Q Fever	SEB	Tularemia
AMedP-8 (Biological) Methods Report	X	X	X	X	X
Consequence Analytic Tools for NBC Operations			X	X	X
Medical Aspects of Biological Warfare	X	X	X	X	X
JAMA Consensus Statement Articles					X

An earlier modeling effort sponsored by the Defense Special Weapons Agency (DSWA) (now the Defense Threat Reduction Agency (DTRA)) developed a febrile performance methodology for three agents for which experimental human data were available. This methodology served as the foundation for the human response methodology used in the previous version of AMedP-8, and is documented in a report titled *Consequence Analytic Tools for NBC Operations, Volume 1: Biological Agent Effects and Degraded Personnel Performance for Tularemia, Staphylococcal Enterotoxin B (SEB) and Q-Fever*.[5] As the title states, this report addresses three of the five new agents of interest, focusing specifically on the effects of inhalation exposure on the warfighter. Data utilized in this report were derived from cases of accidental exposure,

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3 George H. Anno et al., *Biological Agent Exposure and Casualty Estimation: AMedP-8 (Biological) Methods Report*, GS-35F-4923H (Fairfax, VA: General Dynamics Advanced Information Systems, May 2005).

4 Anno et al., *AMedP-8 (Biological) Methods Report*, 2.

5 George H. Anno and Arthur C. Deverill, et al., *Consequence Analytic Tools for NBC Operations, Volume 1: Biological Agent Effects and Degraded Personnel Performance for Tularemia, Staphylococcal Enterotoxin B (SEB) and Q Fever*, DSWA-TR-97-61-V1 (Washington, DC: Defense Special Weapons Agency, October 1998).

naturally acquired infections, and controlled human studies conducted during the 1950s and 1960s.

The third of the "capstone" documents, *Medical Aspects of Biological Warfare*,[6] a volume in the Textbooks of Military Medicine series, devotes an entire chapter to each of the five agents, detailing nearly all aspects of the clinical disease to the extent known at the time of publication in 2007. Each chapter in this book includes a heavily referenced literature review conducted by one or more subject matter experts in specific diseases. In addition to data on the clinical manifestation of each disease in humans, *Medical Aspects of Biological Warfare* also presents information on the diagnosis and treatment of disease, prophylaxis options, and the use of the agent as a biological weapon. This document was used to identify authoritative sources of data for use in populating various submodels, including primary source data where possible.

As shown in Table 3, of the five new agents modeled, tularemia is the only one incorporated in the last of the "capstone" documents. From 1999 to 2002, the *Journal of the American Medical Association* (JAMA) published six articles describing the implications of biological agents attacks against civilian populations. The first five articles featured anthrax, smallpox, plague, botulinum toxin, and tularemia, and the last article spanned several hemorrhagic fever viruses. Authored by over twenty subject matter experts (SMEs), these articles are comprehensive in both the scope of knowledge presented and the breadth of expertise from which it was drawn.

Together, these four "capstone" documents not only provided a comprehensive overview of the human response to each agent, but also served as a starting point for gathering the relevant underlying data. In many cases, these sources provided submodel parameters directly, which were most often credited to other references. Whenever possible, original data from the primary sources were located to either confirm the value given in the "capstone" references or else derive an alternative value. Additional data were located by reviewing the references cited in the "capstone" documents and by conducting Internet searches on relevant terms.

The remaining chapters specify the human response parameter values selected for brucellosis, glanders, Q fever, SEB, and tularemia and fully describe their origin. All parameter selections are documented with the aim of allowing those modelers implementing the *AMedP-8(C)* methodology to critique IDA's assumptions and supplement any data gaps with better or newly generated information as it becomes available. For that reason, justifications for all decisions are provided explicitly and gaps of knowledge are identified to aid in future modeling efforts and highlight weaknesses in

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[6] Zygmunt F. Dembek, ed., *Medical Aspects of Biological Warfare*, Textbooks of Military Medicine (Washington, DC: Office of The Surgeon General, U.S. Army Medical Department Center and School, Borden Institute, 2007).

this model. While the authors believe that the parameters selected in this document represent the best possible values for populating the human response submodels at this time, their applicability may need to be reassessed as assumptions change and new data become available in the future.

2. Brucellosis

This chapter presents the proposed human response model parameter values for brucellosis, the first of five agents discussed in this document. It describes the results of the literature review and data analyses conducted by the IDA study team in the acquisition and derivation of these values.

A. Background

Brucellosis, also known as undulant fever, is caused by a gram-negative bacterium of the genus *Brucella*. There are four major *Brucella* species which produce brucellosis in humans: *B. melitensis*, prevalent among goats and sheep; *B. abortus*, predominantly found in cattle; *B. suis*, common in pigs; and *B. canis*, naturally found in dogs.[7] The majority of human cases worldwide are caused by *B. melitensis*, although *B. abortus* infection is also somewhat common and occurs over a much larger geographical area, including the United States.[8] *B. melitensis* is more likely to lead to severe complications than the other species,[9] although case reports describe the same general illness from all species. The metric of interest for most submodels appeared to be independent of the species, so case data from patients infected with different species were combined. The infectivity submodel was derived entirely from *B. melitensis* cases only because cases from other species were excluded based on other criteria.

Brucellosis is a zoonotic disease, and contraction by humans is generally the result of close contact with infected animals or their byproducts; consumption of unpasteurized, contaminated milk; or improper laboratory procedure. In fact, the combined general lack of awareness of *Brucella* as a potential biohazard and high risk of aerosol transmission have made brucellosis one of the most commonly acquired laboratory diseases.[10] Although human-to-human transmission has been implicated in at least one case of

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7 J. Staszkiewicz et al., "Outbreak of *Brucella melitensis* Among Microbiology Laboratory Workers in a Community Hospital," *Journal of Clinical Microbiology* 29, no. 2 (February 1991): 287.

8 Jorge C. Wallach et al., "Human Infection by *Brucella melitensis*: An Outbreak Attributed to Contact with Infected Goats," *FEMS Immunology and Medical Microbiology* 19 (1998): 315.

9 F. Jacobs et al., "Brucella Endocarditis: The Role of Combined Medical and Surgical Treatment," *Reviews of Infectious Diseases* 12, no. 5 (September – October 1990): 741.

10 E. Gruner et al., "Brucellosis: An Occupational Hazard for Medical Laboratory Personnel: Report of Five Cases," *Infection* 22, no. 1 (1994): 34.

brucellosis,[11] the spread of disease through such means is generally considered to be very rare.[12] For the purposes of the *AMedP-8(C)* methodology, brucellosis will be treated as a non-contagious disease, and no attempt will be made to quantify the rate of its secondary person-to-person spread.

B. Primary References and Data Sets

Over 250 publications, mostly peer-reviewed journal articles, were reviewed during the development of the brucellosis submodels. No single report was used exclusively for any submodel, nor was any reference applicable to the development of all submodels. As indicated earlier in Table 3, information on brucellosis was included in only two of the four "capstone" documents: *AMedP-8 (Biological) Methods Report* and *Medical Aspects of Biological Warfare*. The brucellosis submodel parameter values presented in this chapter will be compared to those specified in these two documents (when given) and any differences discussed.

C. Infectivity

Although experimental studies on the infectivity of *Brucella* in humans occurred as early as the late 1920's,[13] nearly a century later, a generally accepted human model of infectivity as a function of the inhaled dose of organisms has yet to be developed. Those early human experiments, conducted by Morales-Otero in Puerto Rico on forty volunteers, compared the ability of fourteen different strains of *B. abortus* to infect man through various routes, including ingestion and dermal exposure (to normal and abraded skin). Notably, a dose-response relationship was not recorded, nor was inhalation evaluated as a route of exposure. Since then, naturally occurring and accidental laboratory outbreaks in humans have been documented, yet no dose-dependent human inhalation infectivity data have been recorded. Consequently, the infectivity submodel parameters described in this section are based on dose-dependent data derived from controlled animal studies on the effects of inhalation exposure to *Brucella* organisms.

Upon review of the two "capstone" documents relevant to brucellosis, the level of detail of the infectivity information from the two sources was found to vary from a broad qualitative description to a specific quantitative model. *Medical Aspects of Biological Warfare* states only that brucellae are highly infectious in laboratory settings and by the

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[11] Bruce Ruben et al., "Person-to-Person Transmission of *Brucella melitensis*," *The Lancet* 337 (January 1991): 14–15.

[12] Bret K. Purcell, David L. Hoover, and Arthur M. Friedlander, "Brucellosis," in *Medical Aspects of Biological Warfare*, 187.

[13] P. Morales-Otero, "Further Attempts at Experimental Infection of Man with a Bovine Strain of *Brucella abortus*," *The Journal of Infectious Diseases* 52, no. 1 (January–February 1933): 54–59.

airborne route, but provides no quantitative estimates for the infectivity in humans (or animals).[14] In contrast, *AMedP-8 (Biological) Methods Report* presents an infectivity model derived from inputs for brucellosis provided by subject matter experts (SMEs) s: a median infective dose (ID_{50}) of 14.1 organisms and a probit slope of 8.52 probits/$\log_{10}$ dose. The SMEs reportedly provided the following estimates for infectivity: an ID_{10} of 10 organisms, an ID_{50} of 12 organisms, and an ID_{90} of 20 organisms. However, because the three values were inconsistent with a lognormal distribution of infectivity response, the authors of *AMedP-8 (Biological) Methods Report* derived their values solely from the 10% and 90% KAMI infectivity estimates, assuming a lognormal distribution.

The SME-estimated median infective dose of 12 organisms is referenced to a "swine model" from a Russian journal article[15] and is applicable to particles from 0.3 to 1.5 microns. The cited article actually references these values to a guinea pig study by Druett et al. in 1956.[16] The ID_{10} and ID_{90} values are more difficult to trace to original data; the annex in *AMedP-8 (Biological) Methods Report* provides only a vague statement regarding their origin.

> ID_{10} is likely about 10 organisms as 9 out of 10 organisms are usually killed by the serum complement killing process and so the bottom number is about this. (Gary Splitter, *Brucella* conference, 1992?). Based on their monkey data, it looks like the ID_{90} is about 20 organisms (Richard Borsche [sic], *Brucella* conference, 1997).[17]

It appears that the results presented at the various Brucella conferences have been interpreted to mean that if 20 organisms are inhaled and 90% of those are either not retained or killed in the body (as they were in the serum complement killing process), then the ID_{50} is presumable less than the ID_{90} and must be at least one organism.

During the course of the literature search, many documents, including several references cited in the "capstone" documents, were obtained and reviewed for information relevant to the infectivity of inhaled *Brucella* organisms. Quantitative estimates of the infective dose for humans via aerosol exposure were almost universally reported as ten to 100 organisms, yet only one source indicated the origin of its estimate:

> The low yield of brucellae from kill department air and the evidence that airborne transmission of infection does occur suggest that the minimum

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14 Purcell, Hoover, and Friedlander, "Brucellosis," in *Medical Aspects of Biological Warfare*, 187 and 192.

15 K. G. Gapochko and V. I. Ogarkov, "Effect of the Primary Distribution of the Microbial Aerosol in the Respiratory System on the Size of the Infecting Dose (A Review of the Literature)," *Zh Mikrobiol Epidemiol Immunobiol* 50, no. 9 (September 1973): 3–6.

16 H. A. Druett, D. W. Henderson, and S. Peacock, "Studies on Respiratory Infection. III. Experiments with *Brucella suis*," *The Journal of Hygiene* 54, no. 1 (March 1956): 49–57.

17 Anno et al., *AMedP-8 (Biological) Methods Report*, 288.

> infecting dose by the respiratory route is low for humans. The minimum oral infective dose of *B. abortus* and *B. suis* for guinea pigs is about 10^6 to 10^7 organisms; experimental evidence suggests a comparable minimum oral infective dose for humans. The minimum infecting dose by aerosol or subcutaneous injection of guinea pigs, however, is less than 100 organisms. If a comparable disparity exists for humans, the minimum respiratory infecting dose may also be less than 100 organisms.[18]

Without any experimental human data on the inhalation of *Brucella* organisms, it seems reasonable to assume that the other sources have likewise arrived at their human infectivity estimates by analogy with some animal model. Moreover, in the absence of controlled human exposure data providing either particle size distribution or dose-response data, and by relying upon animal exposure data, it must be assumed that an inhaled dose will produce equivalent responses in humans and animals. As shown in Table 4, infectivity information for a variety of animal models and routes of exposure was found in published journal articles. Although this list is by no means exhaustive, an attempt has been made to identify and locate pertinent articles from which the most applicable data can be selected for use in a human inhalation model.

Table 4. Animal Studies on *Brucella* Exposure in Published Journal Articles

Reference	Animal Models Described	Bacillus Challenge Strain	Route of Exposure
Fabyan, 1912	Cattle	Abortus	Injection
	Guinea Pigs	Abortus	Injection
	Mice	Abortus	Injection
	Monkeys	Abortus	Injection
	Pigeons	Abortus	Injection
	Rabbits	Abortus	Injection
	Rats	Abortus	Injection
Huddleson, 1929	Monkeys	Abortus, Melitensis, Suis	Ingestion
Smith, 1932	Guinea Pigs	Abortus	Injection
Morales-Otero, 1933	Guinea Pigs	Abortus	Injection
Meyer, 1941	Monkeys†	Abortus	Injection
		Melitensis	Inhalation
Elberg, 1948	Guinea Pigs	Abortus, Melitensis, Suis	Injection
		Melitensis, Suis	Inhalation
Henderson, 1952	Guinea Pigs	Suis	Inhalation
Herzberg, 1953a	Goats	Melitensis	Injection

[18] Arnold F. Kaufmann et al., "Airborne Spread of Brucellosis," *Annals of the New York Academy of Sciences* 353, no. 1 (December 1980): 105–14.

Reference	Animal Models Described	Bacillus Challenge Strain	Route of Exposure
	Guinea Pigs	Melitensis	Injection
	Mice	Abortus, Melitensis	Injection
	Monkeys	Melitensis	Injection
Herzberg, 1953b	Guinea Pigs	Melitensis	Injection
	Mice	Melitensis	Injection
Elberg, 1955a	Monkeys†	Melitensis	Inhalation, Injection
Elberg, 1955b	Mice	Melitensis	Injection
Herzberg, 1955	Guinea Pigs	Melitensis	Injection
	Mice	Melitensis	Injection
Druett, 1956	Guinea Pigs	Suis	Inhalation, Injection
Elberg, 1957	Goats	Melitensis	Injection
Elberg, 1958	Goats	Melitensis	Injection
	Guinea Pigs		
	Mice		
Elberg, 1962	Goats	Melitensis	Injection
	Guinea Pigs	Abortus, Melitensis	Injection
	Monkeys†	Melitensis	Inhalation, Injection
McCamish, 1962	Guinea Pigs	Melitensis	Injection
Elberg, 1964	Monkeys†	Melitensis	Inhalation
Morgan, 1966	Goats	Abortus, Melitensis	Inhalation, Injection
Chen, 1969	Rabbits	Abortus, Melitensis, Suis	Injection
	Goats	Melitensis	Conjunctive Route
	Guinea Pigs	Melitensis	Ingestion, Injection
Chen, 1970	Guinea Pigs	Melitensis	Injection
	Mice	Melitensis	Injection
	Monkeys	Melitensis	Injection
Percy, 1972	Monkeys	Canis	Ingestion/Conjunctive Route, Injection
Chen, 1973	Monkeys	Melitensis	Injection
Renoux, 1973	Mice	Abortus	Injection
Chen, 1976	Monkeys	Melitensis	Injection
Meador, 1988	Calves	Abortus	Conjunctive Route
Zhan, 1991	Mice	Abortus	Injection
Crawford, 1996	Mice	Melitensis	Injection
Hoover, 1999	Mice	Melitensis	Intranasal Inoculation
Izadjoo, 2000	Mice	Melitensis	Intranasal Inoculation
Mense, 2001	Mice	Melitensis	Intranasal Inoculation
Bhattacharjee, 2002	Mice	Melitensis	Intranasal Inoculation

Reference	Animal Models Described	Bacillus Challenge Strain	Route of Exposure
Diaz-Aparicio, 2004	Goats	Melitensis	Conjunctive Route
Izadjoo, 2004	Mice	Melitensis	Intranasal Inoculation
Mense, 2004	Monkeys†	Melitensis	Inhalation
Rajashekara, 2005	Mice	Melitensis	Injection
Delpino, 2006	Mice	Abortus	Ingestion, Injection
Grillo, 2006	Mice	Abortus	Injection
Yingst, 2010	Monkeys†	Suis	Inhalation

† Monkey inhalation data was deemed most appropriate for use in a human inhalation model.

Of these eight animal models, monkeys (specifically macaques for the monkey studies in Table 4) are the most similar to humans phylogenetically and have been used extensively as a model for inhalation exposure to several biological warfare agents.[19] In addition, the authors of a recent study concluded that rhesus macaques "proved to be an excellent model for human brucellosis."[20] Consequently, monkeys were deemed the animal model most directly relevant to estimating human response to aerosolized *Brucella* organisms.

Of all the journal articles considered in this review, six (indicated with a cross in Table 4) provided some level of information on *Brucella* inhalation exposure in monkeys. In the earliest of the six reports, a 1941 article by Meyer and Eddie,[21] the authors state that "unpublished experiments by Fleishner and Meyer support the early tests of Horrocks which showed that *B. melitensis* when present in dust may readily infect monkeys." Although the results of the more recent studies were not published,

[19] Roger Van Andel et al., "Clinical and Pathologic Features of Cynomolgus Macaques (*Macaca fascicularis*) Infected with Aerosolized *Yersinia pestis*," *Comparative Medicine* 58, no. 1 (February 2008): 68–75; 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 (2001): 3241–47; James W. Boles et al., "Generation of Protective Immunity by Inactivated Recombinant Staphylococcal Enterotoxin B Vaccine in Nonhuman Primates and Identification of Correlates of Immunity," *Clinical Immunology* 108 (2003): 51–59; Douglas S. Reed et al., "Aerosol Infection of Cynomolgus Macaques with Enzootic Strains of Venezuelan Equine Encephalitis Viruses," *The Journal of Infectious Diseases* 189 (March 2004): 1013–17; and Kathleen H. Rubins et al., "The Host Response to Smallpox: Analysis of the Gene Expression Program in Peripheral Blood Cells in a Nonhuman Primate Model," *Proceedings of the National Academy of Sciences* 101, no. 42 (October 2004): 15190–95.

[20] Samuel L. Yingst, et al., "A Rhesus Macaque (*Macaca mulatta*) Model of Aerosol-Exposure Brucellosis (*Brucella suis*): Pathology and Diagnostic Implications," *Journal of Medical Microbiology* 59 (2010): 724–30.

[21] K. F. Meyer and B. Eddie, "Laboratory Infections Due to Brucella," *The Journal of Infectious Diseases* 68, no. 1 (January-February 1941): 24–32.

Horrocks's experimental results were traced to a 1906 report[22] of the commission on Mediterranean fever led by Colonel David Bruce (after whom this disease was later renamed brucellosis). Horrocks reported (p. 46–48) that a caged monkey exposed to aerosolized dust particles infected with *B. melitensis* once a day for 22 days over the course of a month developed brucellosis. Unfortunately, as the monkey was exposed repeatedly to an unknown amount of agent, these results prove only that it is possible to infect a monkey through inhalation of infected dust particles, but provide no insight on a dose-response relationship.

In contrast, the vaccination experiment by Elberg et al. published in 1955 provides enough information to develop a quantitative dose-response model. Vaccinated and unvaccinated groups of rhesus macaques (*Macaccus rhesus*) were exposed to aerosolized particles of *B. melitensis*.[23] For the unvaccinated group, the article cited an ID_{50} of 1.3 x 10^3 organisms, with a 95% confidence interval between 1.2 and 1.5 x 10^3 organisms. The present authors evaluated the same data (shown in Table 5) using the probit method described by Tallarida[24] and calculated a probit slope of 2.10 probits per logarithm of dose and an ID_{50} of 1.25 x 10^3 organisms, which is consistent with the value reported by Elberg et al. The same paper also reports that ten of ten control monkeys were infected after receiving an inhaled dose calculated to contain 3.6 ID_{50} of the same strain, which corresponds to 4,680 organisms using the ID_{50} calculated by that study's authors.

Table 5. Elberg's Rhesus Macaque Respiratory Exposure Data for *B. melitensis*

B. melitensis **Administered (organisms)**	**Total Animals**	**Animals Infected After 6 Weeks**	**Infectivity**
6×10^2	10	3	30%
9.54×10^2	10	4	40%
1.52×10^3	10	5	50%
1.45×10^4	10	10	100%
1.22×10^5	8	8	100%

22 "Part IV," *Reports of the Commission Appointed by the Admiralty, the War Office, and the Civil Government of Malta, for the Investigation of Mediterranean Fever, Under the Supervision of an Advisory Committee of the Royal Society* (London: Harrison and Sons, February 1906).

23 Sanford S. Elberg et al., "Immunization against *Brucella* Infection: IV. Response of Monkeys to Injection of a Streptomycin-Dependent Strain of *Brucella melitensis*," *The Journal of Bacteriology* 69, no. 6 (June 1955): 643–48.

24 Ronald J. Tallarida, "Quantal Dose-Response Data: Probit and Logit Analysis," in *Drug Synergism and Dose-Effect Data Analysis* (Boca Raton: Chapman and Hall/CRC, 2000).

Among the results of subsequent studies by Elberg et al. published in 1962[25] are those of an aerosol challenge of monkeys (*Cynomolgus philippinensis*) immunized subcutaneously. The five monkeys in the unvaccinated control group all became infected after receiving an inhaled dose of 10,000 cells, a result that is consistent with Elberg's earlier findings, if cells are assumed to be equivalent units to organisms. In yet another study by Elberg et al. in 1964, 800 *B. melitensis* organisms were administered via the aerosol route to six macaques used as controls in a vaccine study.[26] Among these six macaques, the challenge dose produced localized infection in five and generalized infection and positive blood cultures in three.

More recently, Mense et al. sought to develop a nonhuman primate model for inhalation exposure to *B. melitensis* in hopes of later evaluating candidate vaccines against brucellosis.[27] As shown in Table 6, the respiratory doses administered to ten rhesus macaques (including two controls that were not intentionally exposed) were recorded and blood samples taken weekly to determine the number of organisms per milliliter of blood. The authors report that six of the eight inoculated macaques were bacteremic, as supported by the data in Table 6. Although the monkeys inhaling 125 and 255 organisms were not bacteremic, nor did they test positive for bacterial culture in any of the tissue samples collected during necropsy, the authors claim that "both macaques challenge exposed with the lowest dose of inoculums contracted brucellosis."[28]

Interestingly, both control monkeys also appear to have been infected, most likely via reaerosolization of *B. melitensis* organisms from exposed monkeys despite careful air washing of their fur. "[One] macaque [had] positive test results for bacterial culture of blood samples and spleen tissues and the other macaque [developed] antibody titers, indicating infection but to a differing degree."[29] Such findings may call into question the accuracy of the measured doses received by the other monkeys, but we will assume that the documented physiological effects are the result of inhaling the doses listed in Table 6.

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25 Sanford S. Elberg and W. K. Faunce, Jr., "Immunization against *Brucella* Infection. 8. The Response of *Cynomolgus philippinensis*, Guinea-Pigs and Pregnant Goats to Infection by the Rev I Strain of *Brucella melitensis*," *Bulletin of the World Health Organization* 26, no. 3 (1962): 421–36.

26 Sanford S. Elberg and W.K. Faunce, Jr., "Immunization against *Brucella* Infection. 10. The Relative Immunogenicity of *Brucella abortus* Strain 19-BA and *Brucella melitensis* Strain Rev I in *Cynomolgus philippinensis*," *Bulletin of the World Health Organization* 30, no. 5 (1964): 693–99.

27 M. G. Mense et al., "Pathologic Changes Associated with Brucellosis Experimentally Induced by Aerosol Exposure in Rhesus Macaques (*Macaca mulatta*)," *American Journal of Veterinary Research* 66, no. 5 (May 2004): 644–52.

28 Ibid., 650.

29 Ibid., 650.

Table 6. Mense's Macaque Respiratory Exposure Data for *B. melitensis*

Inoculation Dose (organisms)	Bacteremic?
0	Yes
0	No
125	No
255	No
3,040	Yes
3,600	Yes
96,000	Yes
102,000	Yes
145,000	Yes
334,000	Yes

The results of the above study are referenced in two other documents,[30] both of which are recently published book chapters written by Hoover and Borschel, two of the coauthors of the Mense et al. article. Their 2004 chapter concludes that the studies "established an ID_{50} of approximately 10^2 organisms as measured by bacteremia."[31] The 2005 reference confirms that "all animals exposed to at least 1 x 10^3 organisms developed bacteremia,"[32] but further reports that one of the two monkeys exposed to 10^2 (either 125 or 255) organisms was also bacteremic. The authors claim that these data are consistent with the ID_{50} of 1.3 x 10^3 organisms described by Elberg et al. Both book chapters also recount unpublished observations by the authors of four additional monkeys challenged via aerosol with 1 x 10^7 organisms, all of which became bacteremic.

It is worth noting that Richard Borschel, the researcher cited by *AMedP-8 (Biological) Methods Report* as a source for the KAMI estimated ID_{90} of 20 organisms is a coauthor on each of the three reports of the above data, which indicate an ID_{50} of 10^2–10^3 organisms for aerosol exposure to monkeys.

The final article in Table 4 with information regarding inhalation exposure of monkeys, published in 2010, describes an experiment by Yingst et al. in which 12 rhesus macaques were exposed via aerosol to high doses of *B. suis*.[33] Although the individual

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30 David L. Hoover and Richard H. Borschel, "Medical Protection against Brucellosis," in *Infectious Diseases: Biological Weapons Defense: Infectious Diseases and Counterbioterrorism* , edited by L. E. Lindler, F. J. Lebeda and G. W. Korch (Totowa: Humana Press Inc., 2005); and David L. Hoover et al., "Development of New *Brucella* Vaccines by Molecular Methods," in *Brucella: Molecular and Cellular Biology*, edited by Ignacio López-Goñi and Ignacio Moriyón (Norwich: Horizon Bioscience, 2004).

31 Hoover et al., "Development of New *Brucella* Vaccines by Molecular Methods," 375.

32 Hoover and Borschel, "Medical Protection against Brucellosis," 171.

33 Samuel L. Yingst, et al., "A Rhesus Macaque (*Macaca mulatta*) Model of Aerosol-Exposure Brucellosis (*Brucella suis*): Pathology and Diagnostic Implications," *Journal of Medical Microbiology* 59 (2010): 724–30.

doses were not reported, they ranged from 4.90 x 10^8 to 6.48 x 10^8 organisms, with a mean of 5.60 x 10^8 and a standard error of the mean equal to 1.84 x 10^7. On days one, three, five, and seven post-exposure, three animals were sacrificed and several swab and tissue samples were collected from each to determine whether a differential diagnosis of brucellosis would be possible based on the various sample results. *B. suis* was detected in the tracheobronchial lymph nodes of all monkeys, and the positive polymerase chain reaction (PCR) results from most tissue samples provided further evidence of infection for those animals sacrificed later in the experiment.

To determine the most appropriate model of aerosol infectivity, a meta-analysis was performed using the range of monkey data presented above under the assumption that one organism and one cell were equivalent units. The data in Table 5 were augmented with the other dose data point (4,680 organisms) from the 1955 Elberg article, as well as the 1962 Elberg data, the 1964 Elberg data (assuming that the three monkeys with generalized infections were a subset of the five with localized infections and one monkey remained infection-free), and the 2004 Mense data. Since the two control monkeys in the Mense study likely inhaled an unknown, nonzero dose of agent, they were excluded from the data set. Despite the authors' statement to the contrary, the two monkeys receiving doses of 10^2 organisms (125 and 255) were considered to be free of infection, as evidenced by their lack of bacteremic response and their negative tissue cultures in the data reported in the article. All monkeys intentionally exposed in the Mense study were counted as infected, including both monkeys receiving doses of 10^2 organisms (125 and 255), despite the mixed reports on their bacteremia. Since the 2010 Yingst data were given as a range rather than individual doses, all that can be said is that the 12 monkeys received at least 4.90 x 10^8 organisms and all became infected; without more precision, this information provides little additional insight, so it too has been excluded.

Table 7. Monkey Data for Aerosol Exposure to *Brucella* Organisms

Inhaled Dose (organisms)	Monkeys Exposed	Monkeys Infected	Source
125	1	0	Mense, 2004
255	1	0	Mense, 2004
600	10	3	Elberg, 1955
800	6	5	Elberg, 1964
954	10	4	Elberg, 1955
1,520	10	5	Elberg, 1955
3,040	1	1	Mense, 2004
3,600	1	1	Mense, 2004
4,680	10	10	Elberg, 1955
10,000	5	5	Elberg, 1962
14,500	10	10	Elberg, 1955
96,000	1	1	Mense, 2004
102,000	1	1	Mense, 2004
122,000	8	8	Elberg, 1955
145,000	1	1	Mense, 2004
334,000	1	1	Mense, 2004
10,000,000[†]	4	4	Hoover, 2004; Hoover, 2005

[†] This data point was excluded in the final analysis for the reasons described in the text.

The probit method described by Tallarida[34] was used to evaluate the combined data set shown in Table 7. This process begins by estimating a dose-response model based only on those dose values for which the population showed some variation in response. It then incorporates those doses for which the proportion becoming infected was either zero or 100%, adjusting the predicted model to better align with the new data in an iterative process until the fit can no longer be improved. This method also includes a weighting factor based on the number of animals in the study. For example, the 40% rate of infection from the ten monkeys receiving 954 organisms has a greater influence on the final model than the 100% rate of infection from the one monkey inhaling 3,600 organisms.

Ultimately, the challenge dose of 10^7 organisms reported in the two book chapters was excluded from the final analysis. Due to the fact that it was so much greater than the rest of the doses, its inclusion caused an error early in the iterative procedure before a proper fit could be confirmed through convergence. Without this data point, the data in

[34] Tallarida, "Quantal Dose-Response Data: Probit and Logit Analysis."

Table 7 were best fit by a probit slope of 2.58 probits per logarithm of dose and an ID_{50} of 9.49 x 10^2 organisms, which is illustrated in Figure 2.

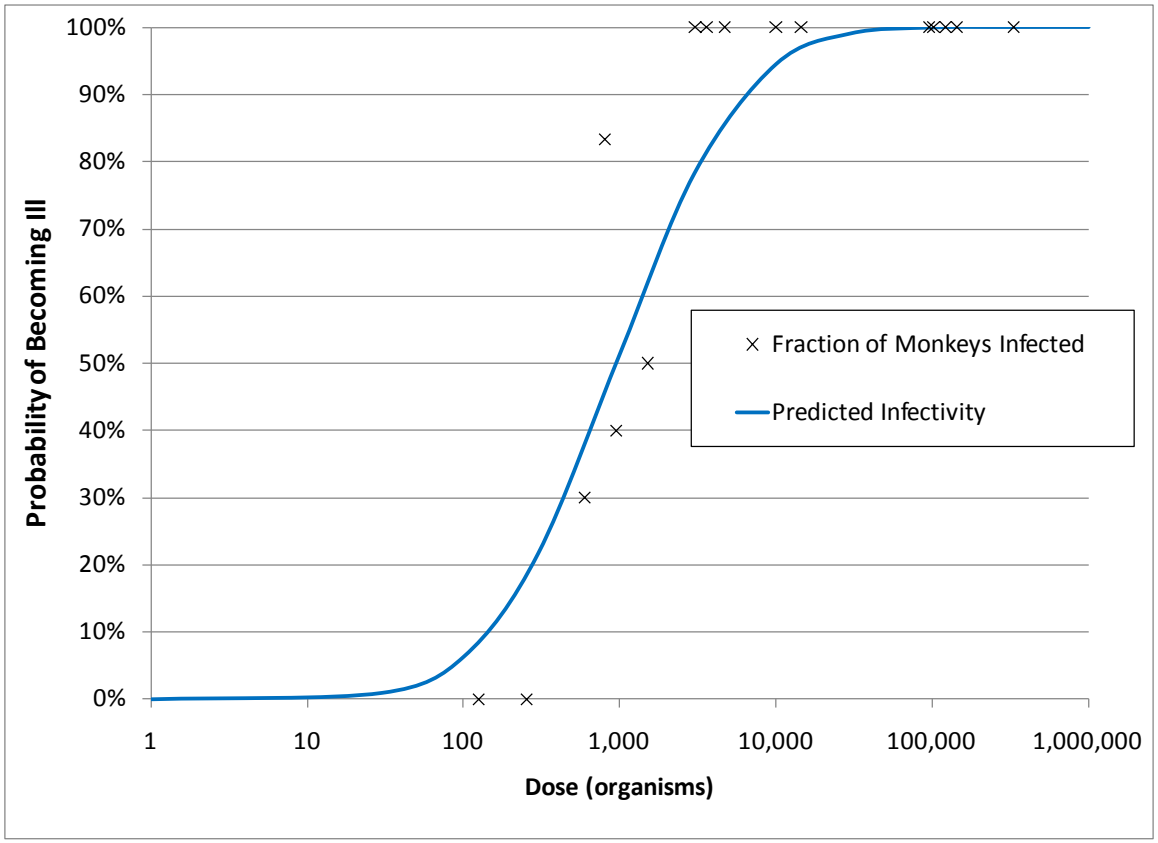

Figure 2. Brucellosis Infectivity Model Fit to Monkey Inhalation Data

This infectivity model is vastly different from that given in *AMedP-8 (Biological) Methods Report*, with a median infective dose of nearly 70 times that given in the "capstone" document and a probit slope of less than a third of the reference value. The ID_{50} value reflects the decision to rely on monkey inhalation exposure data, rather than a combination of guinea pig data and unpublished monkey data which are actually contradicted by the presenter's subsequent published works. The relatively shallow slope of 2.58 probits per logarithm of dose starkly contrasts the steep slope generated by ID_{10} and ID_{90} values of 10 and 20 organisms, respectively, and is reflective of the fact that the data set includes four different doses between 255 and 3,040 organisms that infected only some of the monkeys exposed.

The corresponding cumulative distribution function (CDF) of the lognormal distribution that best fits these data and is used to model the aerosol infectivity of *Brucella* in humans is:

$$F(d) = \frac{1}{2} + \frac{1}{2}\text{erf}\left[\frac{\ln(d) - \mu}{\sigma\sqrt{2}}\right]$$

where:

F is the cumulative fraction of persons who have become infected with brucellosis,

d is the infective dose [organisms],

μ is the mean of the variable's natural logarithm [= $\ln(ID_{50})$ = ln(949 organisms) = 6.86],

m is the probit slope [= 2.58 probits/log(dose)],

σ is the standard deviation of the variable's natural logarithm [= $e^{1/m}$ = $e^{1/2.58}$ = 1.47], and

erf is the error function where $\text{erf}(x) = \frac{2}{\sqrt{\pi}}\int_0^x e^{-t^2}\,dt$.

D. Lethality

Although brucellosis can occasionally be fatal, this is very rare and generally only occurs when the infection resides in the central nervous system or endocardium.[35] Although most brucellosis-induced endocarditis patients die without treatment,[36] this condition occurs in a very small percentage of cases, usually between 1 and 2%.[37] The occurrence of fatalities overall is universally reported to be low, with most references giving a rate below 6%. Yet a large number of symptomatic individuals are never included in the case fatality rate statistics due to underreporting and misdiagnosis, resulting in an even lower probability of death from brucellosis.

The *AMedP-8 (Biological) Methods Report* reports an untreated lethality of less than 5% overall, with specific fatality rates of 3% for *B. abortus* and 6% for *B. suis* and *B. melitensis*, whereas *Medical Aspects of Biological Warfare* does not specify a fatality rate. The published literature supports a low mortality for both treated and untreated cases. In the era before antibiotic treatment, case fatality rates were reported in several studies. In 1930, Hardy reports that 3 of 129 (2.3%) patients in Iowa died.[38] That same year, Simpson's article reported that 1 of 90 (1.1%) cases from Ohio were fatal.[39]

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35 Purcell, Hoover, and Friedlander, "Brucellosis," in *Medical Aspects of Biological Warfare*.

36 Jacobs et al., "Brucella Endocarditis: The Role of Combined Medical and Surgical Treatment."

37 M. R. Hasanjani Roushan et al., "Epidemiological Features and Clinical Manifestations in 469 Adult Patients with Brucellosis in Babol, Northern Iran," *Epidemiology and Infection* 132, no. 6 (2004): 1109–14.

38 A. V. Hardy et al., "Undulant Fever," *Public Health Reports* 45, no. 41 (October 10, 1930): 2433–74.

39 W. M. Simpson, "Undulant Fever (Brucelliasis): A Clinicopathologio Study of Ninety Cases Occurring in and About Dayton, Ohio," *Annals of Internal Medicine* 4, no. 3 (1930): 238–59.

According to Gilbert's 1934 study of cases in New York, there were 6 fatalities in 400 cases (1.5%).[40] A few years later, Baltzan published an article describing seven cases of brucellosis, of which one (14.3%) died, although this patient also had an enlarged liver and serious anemia before contracting brucellosis.[41] Combining these data sets yields an overall case fatality rate of less than 2%. Other accounts provide estimates for the untreated fatality rate of up to 6%.[42] Treated patients have an even higher likelihood of survival.[43]

In addition to the already low lethality figures derived from case fatality rates, several studies have demonstrated that brucellosis is vastly underreported or misdiagnosed, likely due to the non-specific symptoms. One study, published in 1949 by Stoenner et al.,[44] concluded that for every brucellosis case reported in Utah, there are approximately 26 unreported cases. This finding is corroborated by other reports, which have determined the reporting rate of brucellosis to be less than 10%.[45] Since the untreated case fatality rate is likely less than 2% and is almost certainly no greater than 6%, and since most cases are misdiagnosed or unreported, the percentage of individuals that die from brucellosis is likely less than 0.6% of the number who actually become ill.

As stated in the introductory chapter, a fatality rate of less than 1% will be considered negligible and 0% lethality will be assumed for modeling purposes. Considering the already low fatality rate and the extreme underreporting, the authors

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40 Ruth Gilbert and Marion B. Coleman, "Undulant Fever in New York State," *The Journal of Infectious Diseases* 54, no. 3 (May-June, 1934): 305–12.

41 D. M. Baltzan, "Experience with Fifty-Seven Brucellosis Infections in Saskatchewan," *The Canadian Medical Association Journal* 36, no. 3 (1937): 258–62.

42 P. W. Bassett-Smith, "Mediterranean or Undulant Fever," *The British Medical Journal* 2, no. 3228 (1922): 902–5; Alice C. Evans, "Undulant Fever," *The American Journal of Nursing* 30, no. 11 (1930): 1349–52; Louise Hostman, "Undulant Fever," *The American Journal of Nursing* 34, no. 8 (1934): 753–58; P. Bossi et al.,"Bichat Guidelines for the Clinical Management of Brucellosis and Bioterrorism-Related Brucellosis," *Eurosurveillance* 9, no. 12 (2004): 1–5; and Pablo Yagupsky and Ellen Jo Baron, "Laboratory Exposures to Brucellae and Implications for Bioterrorism," *Emerging Infectious Diseases* 11, no. 8 (2005): 1180–85.

43 Marshall D. Fox and Arnold F. Kaufmann, "Brucellosis in the United States, 1965–1974," *The Journal of Infectious Diseases* 136, no. 2 (1977): 312–16; F. Jacobs et al., "Brucella Endocarditis: The Role of Combined Medical and Surgical Treatment," *Reviews of Infectious Diseases* 12, no. 5 (September – October 1990): 740–4.; M. J. Corbel, *Brucellosis in Humans and Animals* (Geneva, Switzerland: World Health Organization, 2006); and Sascha Al Dahouk et al., "Changing Epidemiology of Human Brucellosis, Germany, 1962–2005," *Emerging Infectious Diseases* 13, no. 2 (2007): 1895–1900.

44 Herbert G. Stoenner, Alton A. Jenkins, and E. H. Bramhall, "Studies of Brucellosis in Utah," *The Journal of Infectious Diseases* 85, no. 3 (1949): 213–24.

45 Robert I. Wise, "Brucellosis in the United States: Past, Present, and Future," *The Journal of American Medical Association* 244, no. 20 (1980): 2318; and Al Dahouk et al., "Changing Epidemiology of Human Brucellosis, Germany, 1962–2005," 1898.

have therefore chosen to model brucellosis as a nonfatal disease, thereby supporting the *AMedP-8 (Biological) Methods Report* decision to model a 100% survival rate.

E. Incubation Period

In addition to the animal studies referenced in the infectivity section above, the brucellosis literature includes many cases of human illness acquired during a natural outbreak or through an accidental laboratory exposure. Although these studies lack dose-response information, the progression of disease is usually very well characterized, and when the exact date of exposure can be pinpointed, the incubation period can be determined with a high level of certainty. According to some sources,[46] the length of incubation may depend on the route of exposure. Although no references were provided to support this claim, only cases of inhalation brucellosis were used in the development of the incubation period submodel since many such cases were available and this is the expected route of entry for an intentional attack with biological weapons.

The incubation period associated with brucellosis is highly variable, with reports ranging from a few days to many months. *Medical Aspects of Biological Warfare* reports an incubation period of three days to several weeks, although no source is cited. *AMedP-8 (Biological) Methods Report* provides a dose-dependent incubation period model with a 35 day incubation period for individuals becoming ill after inhaling one organism and a five day incubation period for those inhaling one million organisms. The report states that incubation times are often much longer than this, about two weeks to six months, but decided that a shorter incubation time would better represent an attack scenario. It is not unreasonable to assume that those individuals nearest the point of aerosol attack would inhale very high doses which may result in shorter incubation periods. Nevertheless, such an attack would result in a distribution of doses from very high to very low, and a dose-dependent incubation period model should be independent of the distribution of doses received in a specific scenario.

A review of the literature revealed the extent to which the incubation period is known to vary. The excerpted ranges cited in Table 8 are reflective not only of the highly variable incubation periods, but also of the vast uncertainty that often surrounds each specific case of brucellosis. The incubation period is often difficult to characterize in large part because the exact date or dates of exposure are either unknown or span a considerable time. The sources listed in Table 8 describe cases of human brucellosis

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[46] County of Los Angeles, "Laboratory Exposure to Brucella: Los Angeles County, 1998–1999," in *Department of Health Services Acute Communicable Disease Control Special Studies Report 1999*, 15–18 (Los Angeles: Department of Health Services, 1999); Altoon Dweck, "Emergency Preparedness: Brucellosis," http://www.aahealth.org/physicianslink/bioterrorism_brucellosis_overview.asp; Texas Department of State Health Services, "Brucellosis Information for Professionals," in *Fact Sheet Series* (Austin: Department of State Health Services, 2007).

acquired through consumption of contaminated food, such as unpasteurized dairy products, and via laboratory exposure such as accidental needle-sticks, splashes to the face, and inhalation of aerosols at the workbench.

Table 8. Reports of Incubation Period from Various Articles

Source	Incubation Period Range
Ross, 1906	"The incubation period of Malta fever is somewhere between these two limits [2 and 19 days], certainly not longer." "contracted naturally,…from eight to eleven days"
Bassett-Smith, 1922	"Naturally infected the incubation period is about fourteen days, but by laboratory infection it may be as short as six days"
Simpson, 1930	"found to vary from 5 to 14 days"
Hardy, 1938	[for *B. abortus*] "from 1 week to not less than 4 months, with average intervals much more prolonged than those for *Br. melitensis* infections as ordinarily stated in the literature"
Newitt, 1939	"varies widely" "32 days" [for one individual]
Huddleson, 1940	"a few days to approximately 2 months"
Harris, 1943	"anywhere from a few days to several months" "clinically recognizable illness may not occur for years following exposure"
Trevor, 1959	"usually four to eight weeks"
Young, 1983	"approximately four weeks" [for one individual]
Olle-Goig, 1987	"mean incubation period of 10 weeks (range: five to 14 weeks)"
Staszkiewicz, 1991	"ranging from 6 weeks to over 5 months"
MMWR, 1994	"typically more than 30 days but can range from 5 days to several months"
Young, 1995	"Symptoms are nonspecific, generally occurring within 2–3 weeks of inoculation."
Arlett, 1996	"between two and eight weeks"
Bigler, 1999	"can be less than a week to more than 2 months"
County of Los Angeles, 1999	"average incubation period is 3 to 4 weeks, but instances of up to 10 months have been reported"
Fiori, 2000	"ranged from 6 weeks to 5 months"
FM8-284, 2000	"varies from 5 days to 8 weeks, usually 2 to 8 weeks"
CDC, 2001	"highly variable, ranging from 5 days to 2 months"
Memish, 2001a	"6 weeks to 5 months"
Memish, 2001b	"usually 1–3 weeks, but sometimes it may be several months"
AMA, 2002	"5-60 days (usually 1-2 months)"
Doganay, 2003	"varies between 1 and 5 weeks"
Reguera, 2003	"normally from 2 to 6 weeks, though it may occasionally be much longer"
Bossi, 2004	"highly variable, from one to 60 days, up to several months, with an average of 1-2 months"
Merck Manual, 2005	"varies from 5 days to several months and averages 2 wk"
Pappas, 2005	"usually ranges from two to four weeks"
Yagupsky, 2005	"variable incubation period ranging from <1 week to several months

Source	Incubation Period Range
	(usually 2–4 weeks)"
Corbel, 2006	"The disease is acute in about half the cases, with an incubation period of two to three weeks. In the other half, the onset is insidious, with signs and symptoms developing over a period of weeks to months from the infection."
Kamboj, 2006	"extremely variable, ranging from 5-60 days"
Massachusetts Department of Public Health, 2006	"highly variable, ranging from 5–60 days; illness most commonly occurs about 1 month after exposure"
Pappas, 2006	"relatively protracted,…ranging 9–60 days"
Al Dahouk, 2007	"varied extremely, ranging from a few days to 24 months (median 4 weeks)"
Center for Food Security & Public Health, 2007	"The incubation period is difficult to determine in humans, but has been estimated at five days to three months. Most infections seem to become apparent within two weeks. Aerosolization of bacteria in biological weapons could result in a shorter incubation period."
Mantur, 2007	"usually between seven days and three months, although as long as 10 months have been reported"
Priest, 2008	"ranges from weeks to months" probable cause: "ingesting a soft, herbed cheese imported from El Salvador 2 months before the onset of symptoms"
Maloney, 2009	"relatively long and variable incubation period (1-8 wk)"
Seleem, 2010	"normally is 1-3 weeks, but it can be several months before showing signs of infection"

Since inhalation is the expected route of exposure for individuals attacked with biological weapons, only inhalation exposure cases were considered for use in the incubation period submodel. Seventy-four cases of inhalation exposures were extracted from 11 reports of laboratory outbreaks or isolated accidents. Nine of these articles described cases caused by *B. melitensis*; one article, written by Fiori et al.,[47] characterized an incident of exposure to *B. abortus*; and one, composed by Trever et al.[48] reported a combination of cases caused by *B. melitensis* and *B. suis*. Since the incubation periods were similar following exposure to any of these three species, all were used in a meta-analysis under the assumption that the incubation period is independent of the species of *Brucella* organism. In some cases, interpretation of the data from these 11 articles was necessary before they could be incorporated. For instance, the majority of incubation periods were reported in units of weeks, so those expressed in other units were

[47] Pier-Luigi Fiori et al., "*Brucella abortus* Infection Acquired in Microbiology Laboratories," *Journal of Clinical Microbiology* 38, no. 5 (May 2000): 2005–6.

[48] Robert W. Trever et al., "Brucellosis I. Laboratory-Acquired Acute Infection," *American Medical Association Archives of Internal Medicine* 103, no. 3 (March 1959): 381–97.

rounded to the nearest whole week for the sake of a consistent level of precision in the dataset. After summarizing each report and explicitly detailing any data manipulation performed, the authors will present a summary table (see Table 11) of all 74 data points and describe the derivation of a model for the duration of the incubation period following inhalation exposure to *Brucella* organisms.

The earliest report found to contain incubation period data for inhalation exposures was a 1959 article written by Trever et al. summarizing 60 cases of acute brucellosis. For 21 of these patients, a specific laboratory accident was known to have occurred prior to symptom onset, from which the incubation period was determined. Rather than listing the incubation period for each particular case, however, the article provided the frequency of patients within one of six ranges of incubation periods, as shown in the first two columns of Table 9. In order to use these data, the cases within each range were assumed to be distributed evenly across that range. For instance, six individuals fell within the incubation period range spanning two to four weeks, so this range was divided into six even intervals and one case was assumed to occur at the end of each interval. To match the precision of the meta-dataset, these values were rounded to the nearest whole week value as shown in the last column of Table 9. This distribution of the 21 cases results in a mean incubation period of 6.05 weeks, which is consistent with the mean value reported by Trever et al. of six weeks.

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Table 9. Trever et al. Incubation Period Data

Case #	Incubation Period Range (Weeks)	Distributed Incubation Period (Weeks)	Rounded Incubation Period (Weeks)
1	0–1	0.50	1
2	0–1	1.00	1
3	1–2	1.50	2
4	1–2	2.00	2
5	2–4	2.33	2
6	2–4	2.67	3
7	2–4	3.00	3
8	2–4	3.33	3
9	2–4	3.67	4
10	2–4	4.00	4
11	4–8	4.57	5
12	4–8	5.14	5
13	4–8	5.71	6
14	4–8	6.29	6
15	4–8	6.86	7
16	4–8	7.43	7
17	4–8	8.00	8
18	8–16	10.67	11
19	8–16	13.33	13
20	8–16	16.00	16
21	16–18	18.00	18
		Mean Incubation Period:	**6.05**

In 1983, Young reported ten cases of brucellosis,[49] the majority of which resulted from ingestion of contaminated dairy products or from an unknown source. Three laboratory-acquired cases, however, were presumed to be inhalation exposures. Only one of these patients (Case 3) experienced an overt contamination when he accidentally sprayed his face with a suspension of *B. melitensis*, leading to symptoms approximately four weeks later. Incubation periods for the other two cases were unspecified.

Twenty-two cases of acute brucellosis infection in Spain were reported by Olle-Goig and and Canela-Soler in their 1987 article.[50] Laboratory personnel were assumed to

[49] Edward J. Young, "Human Brucellosis," *Reviews of Infectious Diseases* 5, no. 5 (1983): 821–42.

[50] Jaime E. Olle-Goigand and Jaime Canela-Soler, "An Outbreak of *Brucella melitensis* by Airborne Transmission Among Laboratory Workers," *American Journal of Public Health* 77, no. 3 (March 1987): 335–38.

have been exposed during the manufacturing of a brucellosis vaccine during the first week of June 1982, and their symptom onset was recorded by week, with cases appearing from 6 to 15 weeks after exposure.

Another four cases were reported from Saudi Arabia by Al-Aska and Chagla in 1989. "Case 1 probably acquired infection by direct inhalation, as well as by mucus membrane contact with the organism due to splashing on the face from a positive culture bottle. Cases 2 and 3 acquired infection probably by inhaling contaminated aerosols while working on an open bench. Case 4 acquired infection by needlestick injury to the hand from a needle containing synovial fluid from a patient with brucellosis."[51] Cases 1 and 4 were disregarded because the route of exposure was not solely inhalation, and the Case 3 description included no information on the incubation period. Only the value of two weeks reported for Case 2 was included among the data used in the incubation period submodel.

In their 1991 article, Staszkiewicz et al. reported that in the last two days of March 1988, a frozen *Brucella* isolate was thawed and handled on an open workbench, exposing at least eight individuals who later developed brucellosis.[52] The first case manifested approximately six weeks after this presumed exposure, while the remaining seven cases were described only by the month of onset. For these seven cases, the dates of symptom onset were distributed evenly across the month, as was done above for the Trever et al. data. Table 10 shows the raw data presented in the Staszkiewicz et al. article, along with the assumed dates of onset and the corresponding incubation period in weeks after the exposure date of March 31, 1988.

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[51] Abdul Karim Al-Aska and Abdul Hamid Chagla, "Laboratory-Acquired Brucellosis," *Journal of Hospital Infection* 14, no. 1 (1989): 70–71.

[52] Staszkiewicz et al., "Outbreak of *Brucella melitensis* among Microbiology Laboratory Workers in a Community Hospital."

Table 10. Staszkiewicz et al. Incubation Period Data

Case #	Month of Onset	Distributed Dates of Onset	Rounded Incubation Period (Weeks)
1	May	N/A[†]	6
2	June	15-Jun-88	11
3	June	30-Jun-88	13
4	July	31-Jul-88	17
5	August	10-Aug-88	19
6	August	20-Aug-88	20
7	August	31-Aug-88	22
8	September	30-Sep-88	26

[†] The article explicitly stated a six-week incubation period for this case.

Gruner et al.[53] report five cases of laboratory-acquired brucellosis, of which three characterize the incubation period. Two lab technicians (Cases 3 and 5) first developed symptoms two months after working with strains of *Brucella* from an infected patient, and one (Case 4) presented to the hospital four months after contact with the same strain. By rounding the number of days in two and four months to the nearest number of weeks, the authors included these three cases as data points at 9 and 17 weeks.

In 2000, Fiori et al. reported an outbreak of brucellosis among 12 laboratory workers resulting from a known accidental exposure, with incubation times "ranging from six weeks to five months."[54] The exact dates of symptom onset were given for seven workers, and for the remaining five individuals, only the dates of their first positive antibody titers indicating infection were provided. The authors were less specific, however, when reporting the date of exposure, stating simply that it occurred during the first week of October, 1990.

Using the seven cases with known dates of symptom onset, an analysis was conducted to determine the sensitivity of the incubation periods to a variable exposure date ranging from Monday to Friday. When values were rounded to whole weeks, the set of seven incubation periods was the same for exposure dates of Tuesday through Thursday. Since Wednesday, October 3, 1990, was representative of the majority of the workdays and it was the middle of the week, it was assumed that this day would best approximate the actual exposure date.

In order to use the five cases without specific dates of symptom onset, an assumption would have to be made regarding the time between the first positive antibody

[53] E. Gruner et al., "Brucellosis: An Occupational Hazard for Medical Laboratory Personnel: Report of Five Cases," *Infection* 22, no. 1 (1994): 33–36.

[54] Fiori et al., "*Brucella abortus* Infection Acquired in Microbiology Laboratories," 2005.

titer and the onset of symptoms. For the four patients (among the first seven) for whom both dates were known, this time ranged from two to five days. Therefore it was assumed that the remaining five individuals would likewise manifest symptoms at some time during that range of days after the first positive anti-*Brucella* titer. It was determined through another sensitivity analysis that for an October 3 exposure date, the incubation periods were not sensitive (to the level of weeks) to the difference between two and five days. In other words, using either end of the range resulted in the same estimates for incubation period, when rounding to the nearest whole week value. The authors incorporated all 12 cases under the above assumptions.

Seven cases are reported by Memish and Mah from Saudi Arabia in 2001.[55] The time of exposure was known with relative confidence only in two cases (Case 2 and Case 3). In Case 2, a microbiology technologist became ill 13 weeks after sniffing a specimen later proven to be *B. melitensis*. In Case 3, another technologist developed symptoms 18 days (rounded to three weeks) after thawing samples of *Brucella* isolates to check their viability. The remaining cases were excluded because either no known date of exposure was described or else two possible exposure periods were provided, creating uncertainty in the correct duration of the incubation period.

The two cases of brucellosis described in the 2004 article by Noviello et al.[56] resulted from the misidentification of positive blood cultures and their subsequent handling without the proper safety precautions. In the first case, a laboratory worker processed a patient's blood culture specimen on an open bench, and approximately five weeks later, she become symptomatic. Upon her admission to the hospital, a blood culture specimen was taken and subsequently examined by a second lab worker under the same working conditions, who similarly developed illness two months (nine weeks) later.

Twenty-six laboratory workers were potentially exposed in the accident described by Robichaud et al. in their 2004 article.[57] Ten weeks after the exposure, one individual who had refused antibiotic prophylaxis became symptomatic, while the remaining individuals remained symptom free.

In the final and most recent case report of laboratory-acquired brucellosis, Demirdal and Demirturk describe three cases of exposure to the same *Brucella* samples, although only for one of the three workers was the time of exposure given relative to the onset of

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55 Ziad A. Memish and M. W. Mah, "Brucellosis in Laboratory Workers at a Saudi Arabian Hospital," *American Journal of Infection Control* 29, no. 1 (2001): 48–52.

56 Stephanie Noviello et al., "Laboratory-Acquired Brucellosis," *Emerging Infectious Diseases* 10, no. 10 (2004): 1848–50.

57 Sophie Robichaud et al., "Prevention of Laboratory-Acquired Brucellosis," *Clinical Infectious Diseases* 38, no. 12 (June 15, 2004): e119–22.

symptoms.[58] In this case, the contact with the samples occurred two weeks prior to symptom onset.

The 74 data points from the 11 articles described in this section are summarized in Table 11. The range of incubation period durations in this dataset extends from 1 to 26 weeks, with the middle 50% of cases manifesting symptoms between 6 and 13 weeks after exposure. Several distributions were fit to the data using @RISK software,[59] and the root mean square error was used to determine the most appropriate model. By this measure, a Weibull distribution with a mean of 9.09 weeks and standard deviation of 5.45 weeks was the found to be the best fit. The characteristic parameters for this Weibull distribution, as output by @RISK, were shape parameter = 1.72 and scale parameter = 10.2. The incubation period of inhalation brucellosis was therefore modeled using a Weibull distribution whose corresponding CDF is:

$$F(t) = 1 - e^{-(t/\beta)^{\alpha}}$$

where:

F is the cumulative fraction of persons with brucellosis who have completed the incubation period and become ill,

t is the time post exposure [weeks],

α is the shape parameter [= 1.72], and

β is the scale parameter [= 10.2].

[58] Tuna Demirdal and Nese Demirturk, "Laboratory-Acquired Brucellosis," *Annals Academy of Medicine* 37, no. 1 (2008): 86–87.

[59] *@Risk for Excel: Risk Analysis Add-in for Microsoft Excel*, Version 5.5.1: Professional Edition (Palisade Corporation, 2010).

Table 11. Summary of 74 Cases of Laboratory-Acquired Inhalation Brucellosis in Humans

Case	Incubation Period (Weeks)	Case	Incubation Period (Weeks)	Case	Incubation Period (Weeks)
Trever, 1959		**Olle-Goig, 1987**		**Gruner, 1994**	
1	1	6	7	1	9
2	1	7	8	2	9
3	2	8	8	3	17
4	2	9	9	**Fiori, 2000**	
5	2	10	10	1	6
6	3	11	10	2	6
7	3	12	10	3	6
8	3	13	11	4	10
9	4	14	11	5	10
10	4	15	13	6	10
11	5	16	13	7	10
12	5	17	13	8	11
13	6	18	13	9	14
14	6	19	14	10	14
15	7	20	14	11	14
16	7	21	15	12	24
17	8	22	15	**Memish, 2001**	
18	11	**Al-Aska, 1989**		1	3
19	13	1	2	2	13
20	16	**Staszkiewicz, 1991**		**Noviello, 2004**	
21	18	1	6	1	5
Young, 1983		2	11	2	9
1	4	3	13	**Robichaud, 2004**	
Olle-Goig, 1987		4	17	1	10
1	6	5	19	**Demirdal, 2008**	
2	6	6	20	1	2
3	7	7	22		
4	7	8	26		
5	7				

This CDF is plotted in Figure 3 along with the cumulative fraction of individuals completing the incubation period and manifesting symptoms observed for each week after exposure. The close match between the raw data and the fitted model demonstrates visually that the Weibull function represents the 74 cases quite well.

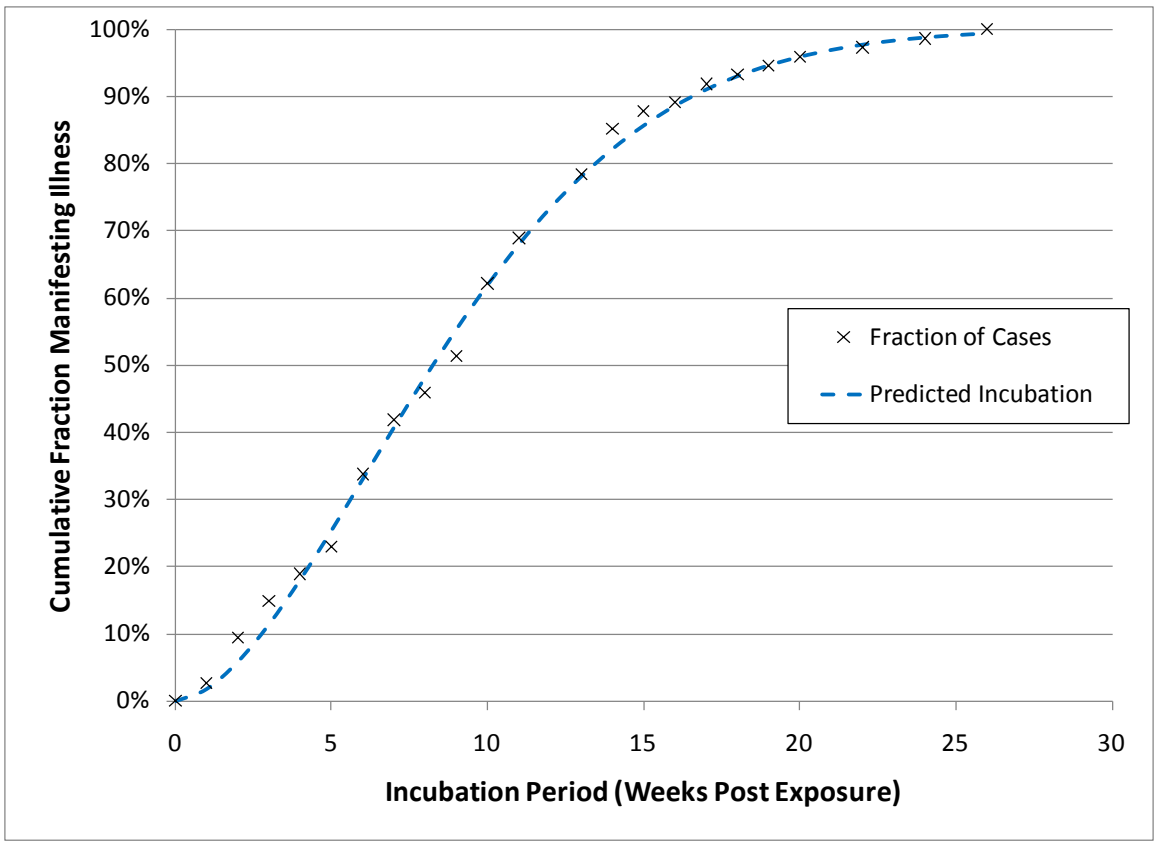

Figure 3. Brucellosis Incubation Period Data and Model Fit

Clearly the range of incubation periods from which the authors derived their model far exceeds the ranges selected by the two "capstone" documents. In fact, over 75% of the cases found in the literature reported incubation periods beyond five weeks, the upper bound in the dose-dependent *AMedP-8 (Biological) Methods Report* model. On the other hand, this dataset does support the alternate range cited by this "capstone" document of two weeks to six months. While the authors understand that the incubation period may indeed be dose-dependent (which may help explain the wide range of incubation periods), without quantitative dose estimates from any of the cases considered, they could not support the implementation of a dose-dependent model.

F. Illness Profile

The symptoms of brucellosis, although nonspecific in nature, are well characterized in the literature. Several review articles have summarized hundreds of cases used to develop lists of symptoms and their rates of incidence among brucellosis patients.[60]

[60] Fox and Kaufmann, "Brucellosis in the United States, 1965–1974," Corbel, *Brucellosis in Humans and Animals*; Mehmet Doganay and Bilgehan Aygen, "Human Brucellosis: An Overview," *International Journal of Infectious Diseases* 7, no. 3 (2003): 173–82; Roushan et al., "Epidemiological Features and

Overall, the presentation of symptoms appears to be independent of the route of exposure[61] as well as the species of *Brucella* organism.[62] Just as the symptoms themselves may vary from one patient to the next, so too do the clinical manifestation and progression of symptoms. Brucellosis cases are classically categorized as acute, subacute, or chronic, based on the duration of symptoms (less than two months, two months to one year, and greater than one year, respectively),[63] although this classification has been criticized as subjective and of limited clinical interest.[64] Regardless of the duration of illness, the onset of disease can be broadly characterized as either abrupt or insidious, so two separate illness profiles have been developed to reflect the variable symptom presentations.

The two "capstone" documents are in general agreement regarding the characterization of the symptoms of brucellosis. *Medical Aspects of Biological Warfare* describes the symptoms of disease as nonspecific, "such as fever, sweats, fatigue, anorexia, and muscle or joint aches."[65] Similarly, the *AMedP-8 (Biological) Methods Report* states that "somatic complaints dominate, with fever, malaise, sweats, headaches, arthralgias, myalgia (particularly in the lower back), anorexia, and weight loss among the symptoms most commonly reported. Other symptoms include chills, asthenia, nausea, vomiting, and constipation."[66] Combining the descriptions from these two documents, the authors have chosen a symptom complex of fever, sweats, chills, headache, malaise, fatigue, arthralgia, myalgia, anorexia, and weight loss to represent this disease. An analysis of nearly 5,000 cases from the literature confirms that these are the most commonly reported symptoms of brucellosis.

According to *Medical Aspects of Biological Warfare*, the disease may be abrupt or insidious in onset.[67] The following description by Hardy illustrates the extent to which the two extreme manifestations of symptom onset can vary.

> So mild were the symptoms in some of the cases that it became a matter of nice discrimination to distinguish the sick man from the mere pretender. On the other hand, the patient sometimes appeared to have been

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Clinical Manifestations in 469 Adult Patients with Brucellosis in Babol, Northern Iran," and Abdul Rahman M. Mousa et al., "The Nature of Human Brucellosis in Kuwait: Study of 379 Cases," *Reviews of Infectious Diseases* 10, no. 1 (1988): 211–17.

61 Purcell, Hoover, and Friedlander, "Brucellosis," in *Medical Aspects of Biological Warfare*, 189.

62 Georgios Pappas et al., "Brucellosis," *The New England Journal of Medicine* 352, no. 22 (2005): 2330.

63 A. R. Lulu et al., "Human Brucellosis in Kuwait: A Prospective Study of 400 Cases," *Quarterly Journal of Medicine* 66, no. 249 (1988): 39–54.

64 Pappas et al., "Brucellosis," 2329.

65 Purcell, Hoover, and Friedlander, "Brucellosis," in *Medical Aspects of Biological Warfare*, 189.

66 Anno et al., *AMedP-8 (Biological) Methods Report*, 42.

67 Purcell, Hoover, and Friedlander, "Brucellosis," in *Medical Aspects of Biological Warfare*, 189.

> completely prostrated at once by the severity of the onset. However, in many of these the suddenness of the attack was more apparent than real, for a careful inquiry often revealed a previous stage of dyspepsia, debility, and languor.[68]

Reports have shown that the distribution of these cases is split more or less equally, with approximately half the cases taking ill rather suddenly.[69] A review of the cases described above for the incubation period submodel (see Table 11) and some additional pre-antibiotic era case reports that did not include incubation period data[70] turned up 23 cases of brucellosis with a gradual onset and 21 cases which were interpreted as having an abrupt onset, which supports the assumption that the split is roughly even.

As indicated by its former name of "undulant fever," brucellosis is characterized by an irregular febrile pattern that often fluctuates during the day, with temperature typically peaking during the late afternoon or evening.[71] In one review of 1,288 cases, fever was intermittent in 83% of cases with course of fever specified.[72] The undulation can also refer to alternating periods of fever and apyrexia lasting days, weeks, or months that patients sometimes experience.

Such recurring febrile relapses are often seen in brucellosis patients within the first six months after therapy.[73] The relapse symptoms typically mirror those of the initial illness, but are often milder than the original. In one study of human brucellosis cases in Kuwait, 41.4% of patients relapsed within six months of completing antibiotic treatment.[74] In another study of laboratory outbreaks, 5 of the 17 patients had no relapses, 9 had one relapse, 2 had two relapses, and 1 had four relapses.[75] It is possible that the

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68 Hardy et al., "Undulant Fever," 2435.

69 Young, "Human Brucellosis," Edward J. Young, "An Overview of Human Brucellosis," *Clinical Infectious Diseases* 21, no. 2 (1995): 283–89; and Bossi et al., "Bichat Guidelines for the Clinical Management of Brucellosis and Bioterrorism-Related Brucellosis."

70 Gilbert and Coleman, "Recent Cases of Undulant Fever in New York State," George E. Atwood and H.E. Hasseltine, "Undulant Fever in Ware County, Ga," *Public Health Reports (1896–1970)* 45, no. 24 (June 13, 1930): 1343–54.; A. Geoffrey Shera, "Four Cases of Undulant Fever," *The British Medical Journal* 2, no. 3691 (October 3, 1931): 605–7.; and A. V. Hardy, S. Frant, and M. M. Kroll, "The Incubation Period in Undulant Fever," *Public Health Reports* 53, no. 20 (1938): 796–803.

71 Philip Manson-Bahr and Hugh Willoughby, "A Critical Study of Undulant Fever," *The British Medical Journal* 1, no. 3561 (1929): 633–35; Gilbert and Coleman, "Recent Cases of Undulant Fever in New York State," and Simpson, "Undulant Fever (Brucelliasis): A Clinicopathologio Study of Ninety Cases Occurring in and About Dayton, Ohio."

72 Fox and Kaufmann, "Brucellosis in the United States, 1965–1974."

73 Hardy et al., "Undulant Fever."

74 A. R. M. Mousa et al., "The Nature of Human Brucellosis in Kuwait: Study of 379 Cases," *Reviews of Infectious Diseases* 10, no. 1 (January – February 1988): 211–17.

75 Calderon Howe et al., "Acute Brucellosis among Laboratory Workers," *The New England Journal of Medicine* 236, no. 20 (May 15, 1947): 741–47.

high rates of relapse in these two studies are related to the choices or application of treatment, as inappropriate or ineffective antibiotic therapy is a known risk factor for relapse.[76] In contrast, recurring undulations of fever occurred in only 11 of 90 cases (12%) reported by Simpson in 1930 before the widespread use of antibiotics, and the vast majority of patients experienced only one febrile period.[77]

As relapses occur in a minority of untreated cases and it is sometimes unclear whether reported illness durations include single or multiple periods of illness, relapses will not be explicitly modeled. Studies reporting that the duration of illness spans two or more distinct episodes of illness surrounding a long period without symptoms were excluded. On the other hand, if the duration was indicated without an explicit statement that relapse was included, it was assumed that the symptoms persisted for the majority of that duration, although a short asymptomatic period may have occurred.

Two distinct illness profiles have been developed for brucellosis to reflect the varying forms of disease onset. For 50% of individuals, brucellosis is modeled with only one stage of illness, which begins abruptly with symptoms of fever, sweats, chills, headache, malaise, fatigue, arthralgia, myalgia, anorexia, and weight loss. As shown in Table 12, this combination of symptoms is designated as Severity Level 3 ("Severe") since the majority of brucellosis patients are admitted to the hospital as inpatients. Although the symptoms often progress throughout the course of the day, diurnal undulations are ignored and a day during which severe symptoms are present in the evening is still considered a day of severe illness.

Table 12. Brucellosis Abrupt Onset Illness Profile

	Stage 1
Signs and Symptoms (S/S)	Fever, sweats, chills, headache, malaise, fatigue, arthralgia, myalgia, anorexia, weight loss
S/S Severity	3 (Severe)
Outlook	Individual will likely recover from illness

[76] Javier Ariza et al., "Characteristics of and Risk Factors for Relapse of Brucellosis in Humans," *Clinical Infectious Diseases* 20, no.5 (May 1995): 1241–49.

[77] Simpson, "Undulant Fever (Brucelliasis): A Clinicopathologio Study of Ninety Cases Occurring in and About Dayton, Ohio."

For the remaining 50% of individuals, the disease is modeled with two stages. These individuals are expected to experience an illness with an insidious onset, so the illness has been divided into two stages. Prior to entering the stage specified in Table 12, individuals will progress through a prodromal stage characterized by symptoms of a lesser severity. The 23 cases found to have an insidious onset offered no useful information regarding which symptoms comprised the initial complex. Atwood characterized the period in nine cases as either "vague" or "prodromal" symptoms. In another study, the differentiation was made between the time to the first symptoms and the time to "severe" symptoms, although these terms were not defined in the text.[78] Ultimately the authors relied on the *AMedP-8 (Biological) Methods Report* when selecting the symptoms for this prodromal stage. The illness profile provided in the "capstone" document began with a four-day period of "some fever and malaise."[79] Likewise, the authors have decided to characterize the first stage of illness in the insidious onset illness profile as Severity Level 1 ("Mild") to reflect the presence of fever and malaise. The full two-stage illness profile is shown in Table 13. This profile more closely resembles the illness profile detailed in the *AMedP-8 (Biological) Methods Report*, which models brucellosis as a disease that begins with mild symptoms and progresses steadily to more severe symptoms.

Table 13. Brucellosis Insidious Onset Illness Profile

	Stage 1	Stage 2
Signs and Symptoms (S/S)	Fever, malaise	Fever, sweats, chills, headache, malaise, fatigue, arthralgia, myalgia, anorexia, weight loss
S/S Severity	1 (Mild)	3 (Severe)
Outlook	Individual will progress to Stage 2	Individual will likely recover from illness

G. Duration of Illness

The duration of the illness is difficult to determine from recent literature since most publications report cases for which antibiotic treatment was provided soon into the illness. Several early papers provide either summary statistics on the distribution of illness duration or specific case histories detailing the course of illness. Such cases were

[78] Hardy, "The Incubation Period in Undulant Fever."

[79] Anno et al., *AMedP-8 (Biological) Methods Report*, 43.

used to determine both the total duration of illness for both illness profiles and also the duration of Stage 1 for the insidious onset illness profile.

Neither "capstone" document relies on solely untreated cases when developing their estimate of the duration of illness for brucellosis. *Medical Aspects of Biological Warfare* describes brucellosis as a disease of three to six month duration that occasionally persists for more than a year.[80] KAMI estimates, which are reported but never used in the *AMedP-8 (Biological) Methods Report*, indicate that the duration of illness could be lifelong without medical treatment, but approximately six weeks to several years with medical treatment.[81]

The duration information actually used in the *AMedP-8 (Biological) Methods Report* is derived from a report of 17 cases by Howe et al.[82] Both references report that the entire duration of illness, including relapses, ranged from four months to one year and that fever (T > 99°F (37°C)) persisted between 13 and 97 days, with an average of 35 days.[83] The authors of the *AMedP-8 (Biological) Methods Report* analyzed the 17 cases to determine the average durations of both the initial episode (21 days) and the first relapse (23.5 days). They did not incorporate relapses into their duration of illness model, so the disease was modeled to last approximately three weeks. It should be noted that the majority of the 17 patients were treated with some form of antibiotic therapy, so the estimated duration accounts for treatment. Moreover, all individuals had been previously vaccinated, and although the vaccine was evidently ineffective at preventing disease, the course of illness could have been altered. Although these cases do have the characteristic recurrence and long duration of brucellosis, they were disregarded from the IDA study team's duration submodel since nearly all patients were treated.

Information on the duration of untreated brucellosis was found in six articles from the pre-antibiotic era. Three of these publications provided only summary statistics of their findings on many cases. In 1922, Bassett-Smith published a report summarizing 522 cases of brucellosis from which he determined that the disease duration ranged from two weeks to two years with an average of four months.[84] In a vaccination study by Hardy in 1930, the average duration of illness among 105 cases of unvaccinated controls was 33.9

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80 Purcell, Hoover, and Friedlander, "Brucellosis," in *Medical Aspects of Biological Warfare*, 189.

81 Anno et al., *AMedP-8 (Biological) Methods Report*, 210.

82 Howe et al., "Acute Brucellosis among Laboratory Workers."

83 Howe et al., "Acute Brucellosis among Laboratory Workers," 744; and Anno et al., *AMedP-8 (Biological) Methods Report*, 42.

84 Bassett-Smith, "Mediterranean or Undulant Fever," 903.

days.[85] Lastly, Simpson studied 90 cases in Dayton, Ohio and estimated the average duration of illness to be approximately four months.[86]

Another set of studies from this time period provided actual case descriptions from which the duration of illness could be determined in some cases. Gilbert and Coleman report 26 cases of brucellosis in New York, although only the first four pages of the article could be obtained, allowing the authors access to 21 cases.[87] From these 21 case reports, nine definitive durations of illness were obtained. In the case where a range of times was given, the midpoint was chosen, and all data points were rounded to weeksin the same manner as the incubation period data. Atwood and Hasseltine published a summary of brucellosis in Ware County, Georgia in 1930, summarizing nine cases, all of which had durations specified in weeks.[88] Finally, four additional cases were documented by Shera in 1931.[89] The data extracted from these three sources is shown in Table 14, along with these values converted into whole week values for use in analysis.

[85] Hardy et al., "Undulant Fever," 2431.

[86] Simpson, "Undulant Fever (Brucelliasis): A Clinicopathologio Study of Ninety Cases Occurring in and about Dayton, Ohio," 248.

[87] Gilbert and Coleman, "Undulant Fever in New York State."

[88] Atwood and Hasseltine, "Undulant Fever in Ware County, Ga."

[89] Shera, "Four Cases of Undulant Fever."

Table 14. Summary of Duration in 22 Cases of Brucellosis

Source	Case	Duration	Rounded Duration (Weeks)
Gilbert, 1928	1	4–5 months	20
	2	2 weeks	2
	3	4 months	17
	4	10 weeks	10
	5	2 months	9
	6	3 months	13
	7	3–4 weeks	4
	8	5 weeks	5
	9	3.5 months	15
Atwood, 1930	1	4 weeks	4
	2	8 weeks	8
	3	8 weeks	8
	4	8 weeks	8
	5	11 weeks	11
	6	11 weeks	11
	7	11 weeks	11
	8	11 weeks	11
	9	20 weeks	20
Shera, 1931	1	16 weeks	16
	2	9 weeks	9
	3	9 weeks	9
	4	7 weeks	7

The median and mean values from this data set are 9.5 and approximately 10 weeks, respectively. The authors used @RISK software to determine the best fit to these data, choosing a gamma distribution on the basis of the root mean square error. The distribution mean (10.1 weeks) and standard deviation (5.05 weeks) are consistent with the sample parameters, and as illustrated in Figure 4, the distribution is an overall good fit to the data.

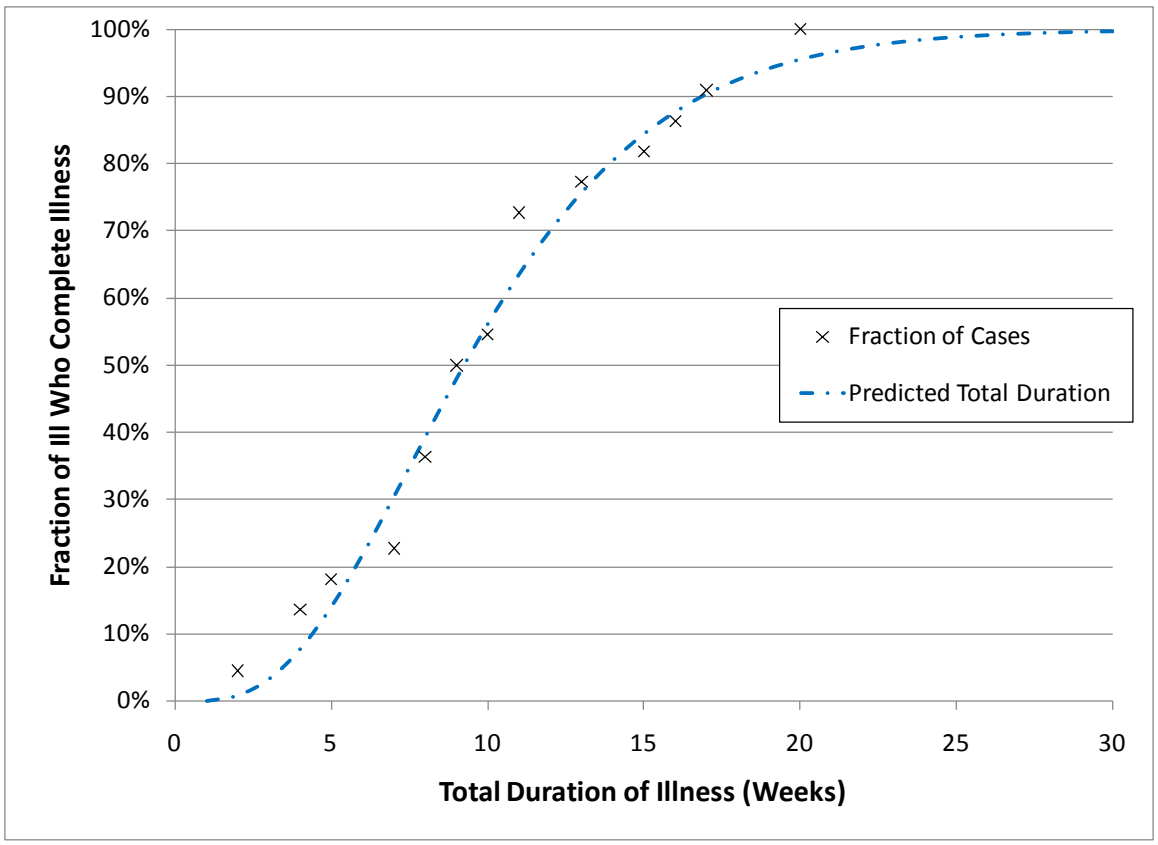

Figure 4. Brucellosis Total Illness Duration Data and Model Fit

The specific gamma distribution parameters output by @RISK were k = 3.9680 and θ = 2.5359. The gamma CDF, which is plotted in Figure 4 along with the cumulative fraction of individuals completed illness, is described by the following function:

$$F(x) = \sum_{i=k}^{\infty} \frac{(x/\theta)^i}{i!} e^{-x/\theta}$$

where:

F is the cumulative fraction of ill persons who become asymptomatic,

x is the duration [weeks],

k is the shape parameter [= 3.97], and

θ is the scale parameter [= 2.54].

Likewise, the duration of Stage 1 for the insidious onset illness profile was derived by reviewing cases from the three articles cited for the total duration, as well as from a 1938 report by Hardy on the incubation period. Hardy's publication provided two dates of symptom onset: one for the earliest symptoms and one for "severe" symptoms. The time between these two onsets can be interpreted as the duration of the prodromal period.

The 20 cases of insidious onset from Hardy and the three older articles are listed in Table 15, and once again, the durations have been rounded to whole week values.

Table 15. Summary of Duration in 20 Insidious Onset Cases of Brucellosis

Source	Case	Duration	Rounded Duration (Weeks)
Gilbert, 1928	1	8 days	1
Atwood, 1930	1	8 days	1
	2	4 weeks	4
	3	2 months	9
	4	2 weeks	2
	5	14 weeks	14
	6	11 days	2
	7	over one month	4
	8	16 days	2
	9	1 month	4
Shera, 1931	1	10 days	1
Hardy, 1938	1	6 days	1
	2	21 days	3
	3	7 days	1
	4	41 days	6
	5	123 days	18
	6	50 days	7
	7	46 days	7
	8	23 days	3
	9	52 days	7

As they did for the total duration of illness, the authors utilized @RISK to determine the duration of Stage 1 of the insidious onset illness profile from the above data. Figure 5 compares the CDF of the chosen gamma distribution to the raw data. The mean duration of Stage 1 predicted by the model (4.41 weeks) and standard deviation (4.84 weeks) are reasonably close to the observed values (4.85 weeks and 5.57 weeks, respectively), and the distribution appears to convincingly represent the durations from the cases cited.

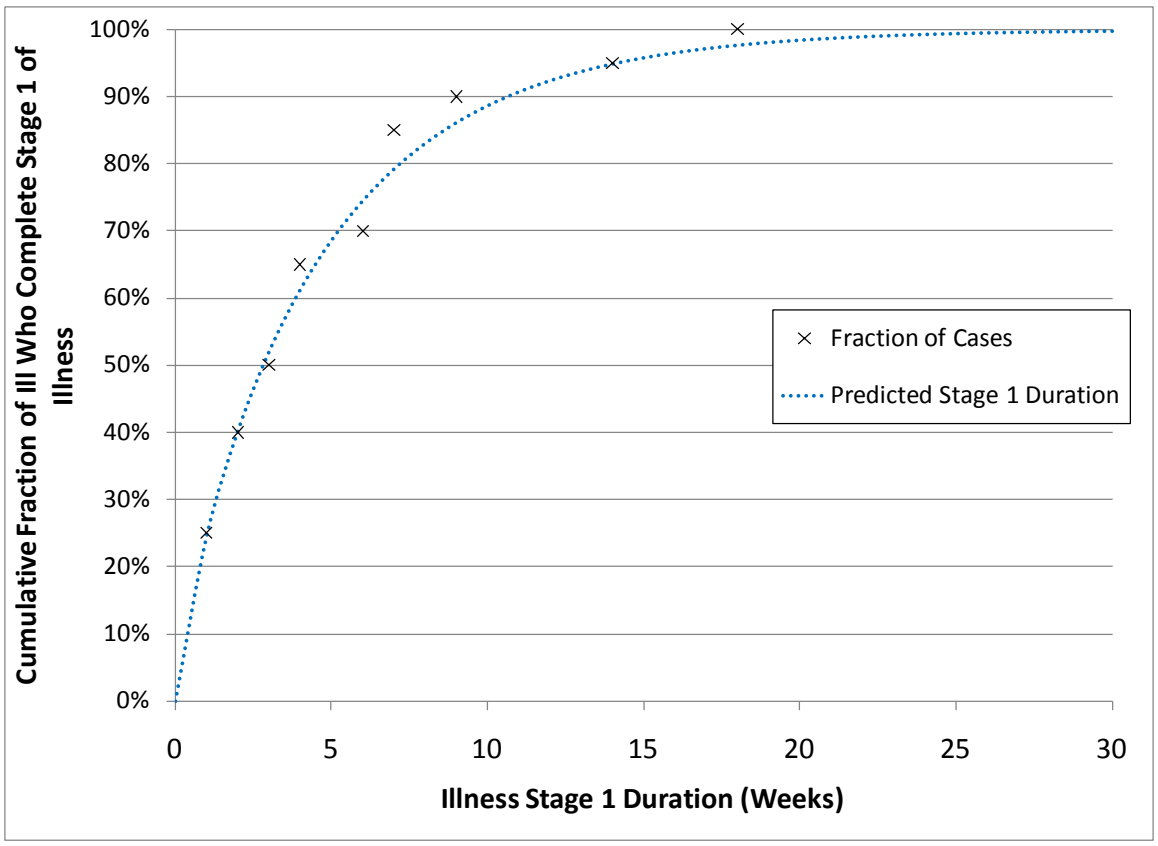

Figure 5. Brucellosis Insidious Onset Stage 1 Illness Duration Data and Model Fit

The parameters of this gamma distribution as output by @RISK were k = 0.82738 and θ = 5.3246. The gamma CDF shown in Figure 5 is characterized by the following function:

$$F(t) = \sum_{i=k}^{\infty} \frac{(x/\theta)^i}{i!} e^{-x/\theta}$$

where:

F is the cumulative fraction of ill persons who have completed the course of disease,

t is the duration [weeks],

k is the shape parameter [= 0.827], and

θ is the scale parameter [= 5.32].

H. Medical Countermeasures and Treatment

As follow-on to the characterization of the infectivity of *Brucella* organisms, the prophylactic effects of vaccination and pre-symptom onset antibiotics were examined. *AMedP-8 (Biological) Methods Report* provided no information about prophylaxis, and at the time of its publication, *Medical Aspects of Biological Warfare* reported that there was no vaccine licensed for use in humans. A review of the literature supported this conclusion, with general agreement that human immunization in the former Soviet Union, China, and France is a thing of the past,[90] although the wording in some sources implies that vaccinations are still employed in these countries.[91] With the bulk of the literature in agreement that no human vaccine is available and without documented results of efficacy trials for those that were used in the past, no vaccination will be modeled.

The most effective treatment of brucellosis in humans appears to be a combined regimen of two antibiotics (typically doxycycline, streptomycin, or rifampin),[92] although the benefit of administering these drugs before the onset of symptoms is unproven.[93] Nevertheless, anecdotal evidence indicates that antibiotic prophylaxis may be effective in preventing disease. In one laboratory case, a culture sample processed mostly on open lab benches was later determined to be *B. melitensis*.[94] Of the six technologists who had directly handled the culture, five accepted antibiotic prophylaxis and remained symptom free. On the other hand, the one technician who refused prophylaxis became ill with brucellosis. Since the exposure environment could not be characterized quantitatively and may have varied among the lab workers, no specific conclusions on the efficacy of antibiotic prophylaxis can be drawn from this report. In the absence of quantifiable efficacy data, neither vaccine nor antibiotic prophylaxis will be modeled for brucellosis.

I. Summary and Conclusions

The parameter values proposed in this chapter for brucellosis were derived from a collection of articles which range from century old studies of outbreaks to

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90 M. J. Corbel, "Brucellosis: An Overview," *Emerging Infectious Diseases* 3, no. 2 (1997): 219; Young, "An Overview of Human Brucellosis," 288.

91 C. P. Hadjichristodoulou et al., "Tolerance of the Human Brucellosis Vaccine and the Intradermal Reaction Test for Brucellosis," *European Journal of Clinical Microbiology & Infectious Diseases* 13, no. 2 (1994): 129–34; Mohamed N. Seleem, Stephen M. Boyle, and Nammalwar Sriranganathan, "Brucellosis: A Re-Emerging Zoonosis," *Veterinary Microbiology* 140, no. 3–4 (2010): 396.

92 Purcell, Hoover, and Friedlander, "Brucellosis," in *Medical Aspects of Biological Warfare*, 190–192; Seleem et al., "Brucellosis: A Re-Emerging Zoonosis," 396.

93 Bossi et al., "Bichat Guidelines for the Clinical Management of Brucellosis and Bioterrorism-Related Brucellosis."

94 Robichaud et al., "Prevention of Laboratory-Acquired Brucellosis," 119–22.

microbiological studies from the past decade. They are not derived from controlled animal exposure experiments which quantify the parameters of interest. It is the recommendation of the authors to use the parameters described above, but to simultaneously pursue a research program to quantitatively characterize the infectivity, lethality, incubation, duration and course of illness of brucellosis.

Based on the available data, analysis and literature review as described in the preceding sections, the authors recommend using the parameter values provided in Table 16 to model brucellosis. Two distinct illness profiles for brucellosis, described in Section F. and repeated here in Table 17 and Table 18, have been developed to accommodate the clinical differences between abrupt and insidious onset of illness; the population of brucellosis patients is expected to be evenly divided among these two profiles.

Table 16. Brucellosis Model Parameters Summary Table

Submodel	Type	Parameters
Infectivity	Lognormal distribution	ID_{50} = 949 organisms, Probit slope = 2.58 probits/log(dose)
Lethality	Case fatality rate	0%
Incubation period	Weibull distribution	$\alpha = 1.72$, $\beta = 10.2$
Duration of illness		
• Total	Gamma distribution	$k = 3.97$, $\theta = 2.54$
• Abrupt onset Stage 1	Same as total	
• Insidious onset Stage 1	Gamma distribution	$k = 0.827$, $\theta = 5.32$
• Insidious onset Stage 2	Total minus Stage 1	

Table 17. Brucellosis Abrupt Onset Illness Profile

	Stage 1
Signs and Symptoms (S/S)	Fever, sweats, chills, headache, malaise, fatigue, arthralgia, myalgia, anorexia, weight loss
S/S Severity	3 (Severe)
Outlook	Individual will likely recover from illness

Table 18. Brucellosis Insidious Onset Illness Profile

	Stage 1	Stage 2
Signs and Symptoms (S/S)	Fever, malaise	Fever, sweats, chills, headache, malaise, fatigue, arthralgia, myalgia, anorexia, weight loss
S/S Severity	1 (Mild)	3 (Severe)
Outlook	Individual will progress to Stage 2	Individual will likely recover from illness

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3. Glanders

This chapter presents the proposed human response model parameter values for glanders, the second of five agents discussed in this document. It describes the results of the literature review and data analyses conducted by the IDA study team in the acquisition and derivation of these values.

A. Background[95]

Glanders is a zoonotic disease of horses, mules, donkeys and other solipeds caused by the bacteria *Burkholderia mallei* (*B. mallei*). It is an ancient disease, first described by Aristotle in 330 BC, and by the nineteenth century glanders was fairly common in animals worldwide. Once diagnostic testing became available by the turn of the twentieth century, eradication programs proceeded in earnest in many nations. The last naturally occurring human case of glanders in the United States was reported in 1934; the disease was officially eradicated from the United States in 1942. Today glanders has been eradicated from most countries, but is still found in parts of Africa, the Middle East, South America, and Eastern Europe.

Most human cases of glanders occur among individuals in occupational and lifestyle settings, such as veterinarians, farriers, slaughterhouse personnel, farmers, and stable hands. *B. mallei* can survive in a wide variety of media common in an equine environment, such as stable bedding, manure, food and water troughs, and even harnesses and tack. Handling of sources like these can transmit the disease by contact with mucous membranes, contact with cuts or abrasions, or inhalation into the lungs.

Glanders occurs in three clinical forms: acute, chronic, and latent. The acute form of glanders is the most common, with a rapid onset, severe signs and symptoms, and a rapid progression usually resulting in death. Chronic glanders is less fatal and has less severe signs and symptoms with intermittent recurrences. Latent glanders is the least documented clinical form because of its similarity to chronic glanders, but with a lengthy incubation period. In addition to different clinical forms, there are several different types of infections. The definition of each type of infection varies from source to source. Most commonly documented types of infection are; localized infection, nasal mucosa infection

[95] The information in this section is summarized from Bridget C. Gregory and David M. Waag, "Glanders," in *Medical Aspects of Biological Warfare*, 121–146.

(which is a sub-form of a localized infection), lung infection and blood infection (bacteremia). Neither the clinical form nor the type of infection are exclusive. One form can potentially cause another and the same can occur with infection types.

B. Primary References and Data Sets

As indicated earlier in Table 3, two of the four "capstone" documents included information on glanders: the *AMedP-8 (Biological) Methods Report* and *Medical Aspects of Biological Warfare*.[96] Additional supporting literature used by the IDA study team for the development of the glanders submodel parameter values included 210 case reports, described in 15 separate documents. Table 19 identifies the additional sources used. The information within these reports was collated and compared against the models and parameter values described in the two "capstone" documents.

Table 19. Glanders Documentation Sources

Year	Author(s)	Number of Cases
1831	John Elliotson	9
1843	Mr. Hamerton	3
1854	W. I. Cox	1
1856	Frederick Mason	1
1904	Clark Stewart	3
1906	George Dougall Robins	152
1907	James Taft Pilcher	2
1908	William Hunting	22
1909	Julius M. Bernstein & E. Rock Carling	6
1933	I. Sobol	1
1933	John Ellitson	1
1936	J. F. Burgess	1
1938	A. A. Herold & C. B. Erickson	1
1947	Calderon Howe & Winston R. Miller	6
2001	A. Srinivasan et al.	1

C. Infectivity

Since glanders has been largely eliminated from the modern world, there is little or no human data available from which to develop an infectivity model. Available literature contains very few data on dose response, and no infectivity values can be calculated

[96] Gregory and Waag, "Glanders," in *Medical Aspects of Biological Warfare*.

directly from case reports. The authors were unable to identify any human dose response test data. This dearth of data makes an estimate of an infective dose difficult to determine.

Medical Aspects of Biological Warfare[97] regards glanders (particularly aerosolized glanders) as highly infectious: it requires very few organisms to cause an infection. The *AMedP-8 (Biological) Methods Report* modeled the probability of becoming infected with glanders as a lognormal probability function with an ID_{50} of 24.5 colony forming units (CFU) and a probit slope of 1.93 probits per logarithm of dose.[98] Given the lack of dose response data in published reports, and given similarities between glanders and tularemia, the probit slope of the glanders infectivity model described in the *AMedP-8 (Biological) Methods Report* was based on tularemia. The authors recommend modeling glanders infectivity as a lognormal distribution with an ID_{50} of 24.5 organisms and a probit slope of 1.93 probits per logarithm of dose. Figure 6 graphically represents the infectivity characteristics of glanders according to dose.

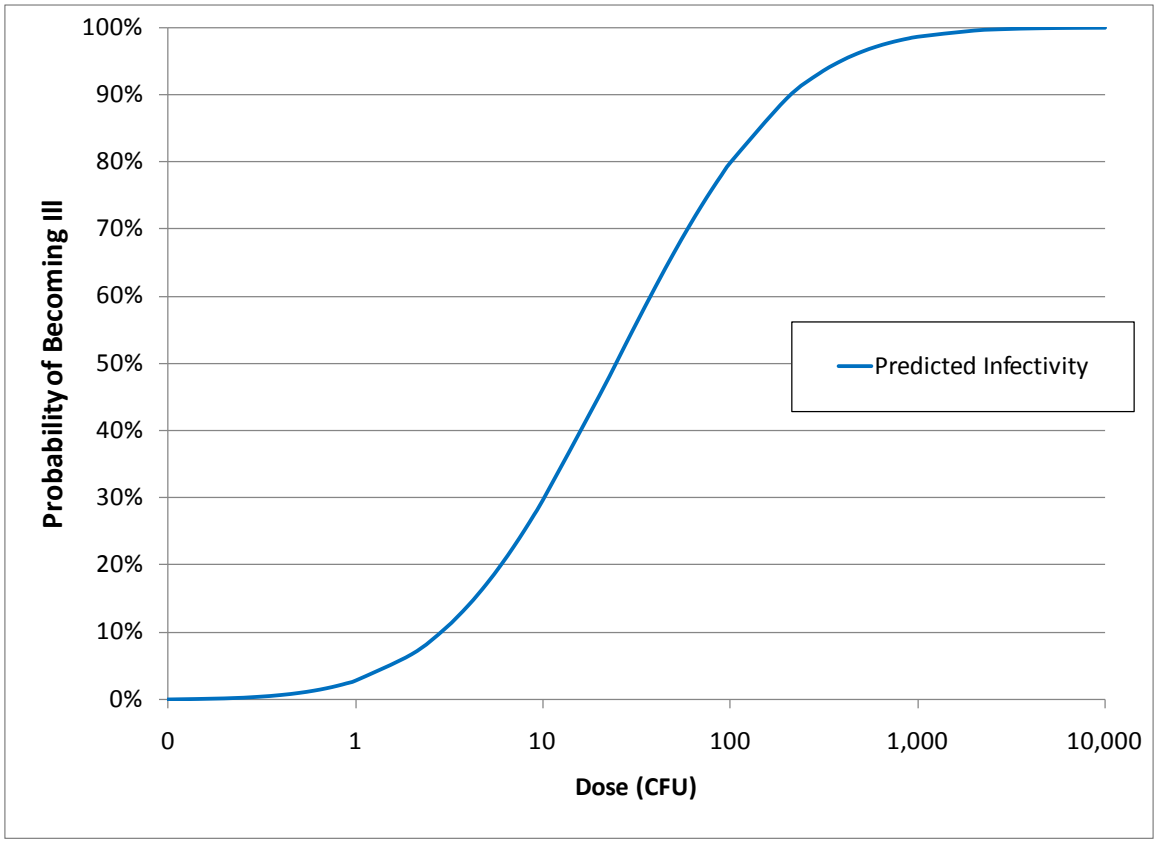

Figure 6. Glanders Infectivity

97 Ibid.

98 Anno et al., *AMedP-8 (Biological) Methods Report*.

The corresponding CDF of the lognormal distribution used to model the aerosol infectivity of glanders in humans is:

$$F(d) = \frac{1}{2} + \frac{1}{2}\text{erf}\left[\frac{\ln(d) - \mu}{\sigma\sqrt{2}}\right]$$

where:

F is the cumulative fraction of persons who have become infected with glanders,

d is the infective dose [CFU],

μ is the mean of the variable's natural logarithm [= $\ln(ID_{50})$ = ln(24.5 CFU) =3.20],

m is the probit slope [= 1.93 probits/log(dose)],

σ is the standard deviation of the variable's natural logarithm [= $e^{1/m}$ = $e^{1/1.93}$ = 1.68], and

erf is the error function where $\text{erf}(x) = \frac{2}{\sqrt{\pi}}\int_0^x e^{-t^2}\,dt$.

Human to human transmission can occur by physical contact with contaminated fluids or materials, but generally has not been observed from aerosol respiration. For example Robins reported that a whole family became infected due to being in close proximity of one another.[99] Similarly, nurses, doctors and scientist have become infected from being in close proximity to infected individuals and matter. Robins reports that as many as 10% of 156 chronic infections he reviewed are from human to human contact.[100] After reviewing all the case reports, it is clear that glanders is rarely human to human contagious. For the purposes of the *AMedP-8(C)* methodology, glanders will be treated as a non-contagious disease, and no attempt will be made to quantify the rate of its secondary person-to-person spread.

D. Lethality

Similarly to the effort to estimate an infective dose, estimation of a lethal dose is hindered by a dearth of published data on dose response, and no lethal dose values can be calculated directly from case reports. *Medical Aspects of Biological Warfare* states that in the human glanders cases that occurred before antibiotics, "over 90% of these people

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[99] George Dougall Robins, *A Study of Chronic Glanders in Man with Report of a Case Analysis of 156 Cases Collected from the Literature and an Appendix of the Incidence of Equine and Human Glanders in Canada*, Vol. 2, No. 1, Studies from the Royal Victoria Hospital Montreal (Montreal: Montreal Guertin Printing Co., 1906).

[100] Ibid.

died," [101] that untreated acute bronchopulmonic or pneumonic glanders was "almost uniformly fatal," [102] and that "mortality rates have been reported to be 95% without treatment."[103] The *AMedP-8 (Biological) Methods Report* assumes 100% lethality.[104] Both of these reports also suggest that with modern medicine, treated glanders is generally survivable, with a case fatality rate of about 50%.

For comparison, these untreated lethality estimates were compared to the data found in the case reports. In Table 20, lethality values were calculated using all case reports, excluding incomplete cases. (Incomplete cases were not considered for an analysis of lethality since no final disease outcome had been determined.) One hundred and fifty-nine case reports were used to estimate the overall lethality of glanders. The untreated lethality was calculated using 152 of the 159 case reports. (The other 7 case reports were treated.).

Table 20. Calculated Glanders Lethality Values

Type of Lethality	Lethality
Overall (159 cases)	66.04%
Untreated (152 cases)	69.08%

From the data gathered, glanders is a highly lethal illness, but not quite the 100% lethal disease described in *Medical Aspects of Biological Warfare* and the *AMedP-8 (Biological) Methods Report*. The authors recommend using a case fatality rate of 70% as an estimate of glanders lethality.

E. Incubation Period

The *AMedP-8 (Biological) Methods Report* models the glanders incubation period as widely varying, with an average time of 10 to 14 days, but as little as 4 days for high doses and as much as a few weeks for low doses.[105] *Medical Aspects of Biological Warfare* characterizes a much broader incubation period of less than a day to several weeks.[106] They break down incubation periods to cutaneous and mucous infection which

[101] Gregory and Waag, "Glanders," in *Medical Aspects of Biological Warfare*, 140.

[102] Ibid., 131.

[103] Ibid., 134.

[104] Anno et al., *AMedP-8 (Biological) Methods Report*, 49.

[105] Ibid., 212.

[106] Gregory and Waag, "Glanders," in *Medical Aspects of Biological Warfare*, 128.

could take a little as 3 to 5 days and an inhalational infection could take two to three weeks.[107]

From all the data collected, only 37 cases contained data with incubation periods. Even though different routes of exposure incubate at different rates, most documented incubation periods are from cutaneous exposures or accidental inoculations. Since there are a limited number of case reports that include incubation periods, all but three data points were used regardless of their route of exposure or clinical form. Two cases were extreme outliers and the third case was too ambiguous to use. From the remaining 34 data points, glanders was calculated to have a mean incubation period of eight days (7.82 days). Table 21 represents the 37 cases that were used to determine the incubation period. After examining the data, there was an additional case that is an outlier, but not as extreme as the other. If this value is excluded the mean incubation period becomes seven days (6.79 days).

Table 21. Documented Glanders Incubation Periods

Source	Incubation Period	Rounded Incubation Period (days)	Note
Eliotson, 1830	3 days	3	
Eliotson, 1830	6 weeks	42	Latent
Cox, 1854	24 hours	1	
Stewart,1904	6 days	6	
Robins,1906	local 6 hours – 4 days	1	
Robins,1906	10+ years?	3650	Outlier
Robins,1906	7 days	7	
Robins,1906	4 days	4	
Robins,1906	12 days	12	
Robins,1906	7 days	7	
Robins,1906	a few days	3	
Robins,1906	under 3 weeks	2	
Robins,1906	48 hours	2	
Robins,1906	24 hours	1	
Robins,1906	15 days	15	
Robins,1906	7 days	7	

[107] Ibid., 131.

Source	Incubation Period	Rounded Incubation Period (days)	Note
Robins,1906	8 days	8	
Robins,1906	a few hours	1	
Robins,1906	48 hours	2	
Robins,1906	24 hours?	1	
Robins,1906	several months	121.7	Outlier
Robins,1906	1 day	1	
Robins,1906	less than 21 days	20	
Robins,1906	1 week	7	
Robins,1906	a few hours	1	
Herold,1938	7 days	7	
Srinivasan, 2001	a few days – several weeks		Too broad
Pilcher,1907	25 days	25	
Pilcher,1907	5 days	5	
Bernstein,1909	9 days	9	
Sobol, 1933	a few days	3	
Howe,1946	12 days	12	
Howe,1946	less than 1 day	1	
Hunting,1908	~ 9 days	9	
Hunting,1908	~ 7 days	7	
Hunting,1908	7 days	7	
Hunting,1908	15 days	15	
	Mean =	6.79 days	
	+ Latent =	7.82 days	
	+ Outliers =	112.16 days	

This mean incubation period of 7 to 8 days generally agrees with the *Medical Aspects of Biological Warfare* value. The *AMedP-8 (Biological) Methods Report* range of 10 to 14 days is higher than the calculated estimate, but the calculation is well within the

AMedP-8 (Biological) Methods Report high to low dose range of four days to a few weeks.[108]

Using the @RISK software tool, a lognormal function was fit to the data in Table 21 and found to have a mean of 8.29 days and a standard deviation of 13.0 days. The corresponding CDF of the lognormal distribution used to model the incubation period for glanders is:

$$F(t) = \frac{1}{2} + \frac{1}{2}\text{erf}\left[\frac{\ln(t) - \mu}{\sigma\sqrt{2}}\right]$$

where:

F is the cumulative fraction of persons with glanders who have completed the incubation period,

t is the time post exposure [days],

μ is the mean of the variable's natural logarithm [=1.50],

σ is the standard deviation of the variable's natural logarithm [= 1.11], and

erf is the error function where $\text{erf}(x) = \frac{2}{\sqrt{\pi}}\int_0^x e^{-t^2}\,dt$.

[108] Anno et al., *AMedP-8 (Biological) Methods Report*, 212.

Figure 7 illustrates the proposed distribution for the glanders incubation period submodel, as well as the underlying data points considered.

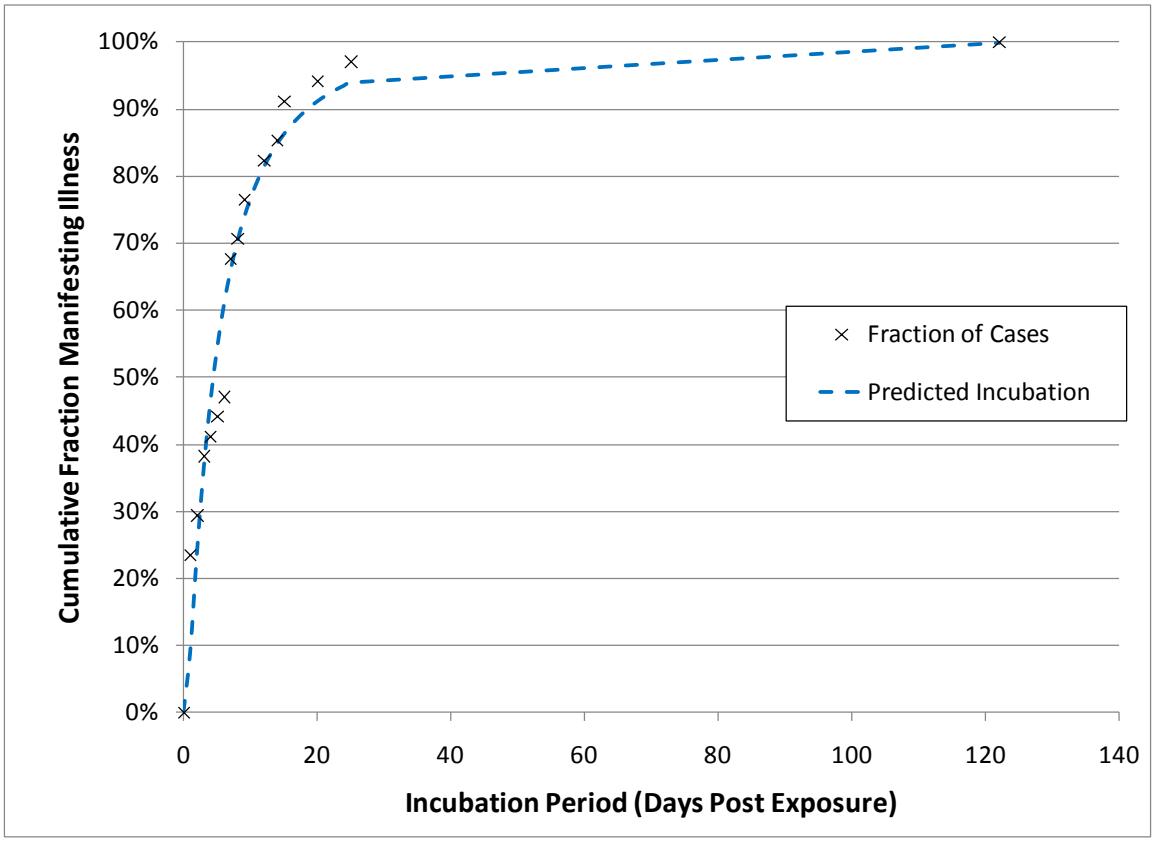

Figure 7. Cumulative Distribution of Documented Glanders Incubation Periods

F. Illness Profile

Both *Medical Aspects of Biological Warfare* and the *AMedP-8 (Biological) Methods Report* contain varying descriptions of the common symptoms experienced from a glanders infection. The *AMedP-8 (Biological) Methods Report* lists the most common symptoms, consisting of abscesses, fever, nasal involvement, pain, skin eruptions, cough, bronchitis, asthenia, oral and pharynx involvement, rigors, emaciation, delirium, ocular involvement, gastrointestinal symptoms, sweating, and insomnia.[109] *Medical Aspects of Biological Warfare* describes the generalized symptoms as consisting of fever, myalgia, headache, fatigue, diarrhea, weight loss, and lymphangitis.[110]

[109] Anno et al., *AMedP-8 (Biological) Methods Report*, 256.

[110] Gregory and Waag, "Glanders," in *Medical Aspects of Biological Warfare*, 122.

The case reports were reviewed to create a list of common signs and symptoms. Each was counted to see how often each symptom occurred out of all the cases to build a common symptom list. Because illness profiles vary so greatly between individuals, even symptoms with relatively infrequent of incidence were considered. At a 10% incidence there are 19 symptoms in common, a 20% incidence results in only 9 common symptoms, and a 30% incidence results in only 3 common symptoms. Table 22 represents the symptoms that have occurred in more than 10% of cases and their occurrence within the reviewed case reports.

Table 22. Occurrences of Over 10% of Common Symptoms

Symptom	Occurrences
Abscesses	57.74%
Swelling	31.55%
Nasal discharge	30.36%
Localized pain and inflammation	29.76%
Pain	28.57%
Ulcerations	27.38%
Chills	26.19%
Phlegmon	25.60%
Pustules	22.02%
Fever	19.64%
Suppuration	19.64%
Cough	16.67%
Red streaks	13.69%
Necrosis	12.50%
Diarrhea	11.90%
Emaciation	10.71%
Papular eruption	10.71%
Delirium	10.12%
Dyspnea (difficulty breathing)	10.12%

The *AMedP-8 (Biological) Methods Report* provides an estimate of when each symptom would occur during the illness. They assumed 100% lethality, so only one illness profile was created. The illness profile starts on the first day the first symptom starts. The first symptoms to appear would be mild, consisting of fever, malaise, loss of appetite, nausea, and headache. Moderate symptoms will arise six days later consisting of painful nodules and swellings on face and limbs in addition to previously stated symptoms. Two weeks into the duration of the illness, additional symptoms arise consisting of pustular eruptions on most of body, nasal mucosa becomes reddened and edematous with ulceration and purulent discharge, and dyspnea may be present. Around

the 17th day the most severe symptoms arise consisting of respiratory problems, muscular abscesses, metastatic pneumonia, diarrhea, severe pyemia with suppurating pustules covering body and emaciation ending terminally. [111]

Medical Aspects of Biological Warfare describes several illness profiles according to the originating manifestation. Focusing mainly on an aerosolized glanders attack, glanders would primarily cause nasal and/or ocular infections and possibly pulmonary infections. The nasal or ocular mucosa infection would produce a localized infection. The infected mucosa would swell and excrete a mucopurulent discharge. Papular and ulcerative lesions may appear with blisters and sores. The nose may swell and become inflamed with copious discharge. Facial swelling is possible along with the infection spreading to the nasal septum and the bony tissue causing fistulae and tissue destruction. Lymph glands may also become inflamed and suppurate. Dissemination would spread the infection further into the body, infecting the respiratory tract and lungs (pulmonary infection). Pulmonary infections would cause tracheitis and bronchitis with cough and mucopurulent sputum production. Other symptoms that can arise include; fever, headache, fatigue, prostration, pneumonia, pulmonary abscess, pleuritis, pleural effusion, cough, dyspnea, chest pain, mucopurulent sputum.[112]

Two illness profiles were created from the data collected: one for survivors and the other for non-survivors. The illness profiles were created using all the above information extracted from the reviewed case reports. Since glanders has varying routes of infectivity, there is no 'standard' illness profile. Symptoms that were experienced in more than 10% of individuals were used to create a 'general' illness profile. Three assumptions were made; an attack of glanders would be by means of an aerosol relase, causing an acute clinical form, and the duration of illness is fitted to the suggested durations of the *AMedP-8 (Biological) Methods Report* and Gregory et al. After the onset of infection, an individual would experience mild symptoms consisting of localized pain and inflammation, fever, swelling, chills, and phlegmon (Stage 1). Following this, the individual would experience more moderate symptoms consisting of cough, suppuration, red streaks, papular eruption nasal discharge, abscess, pain, and ulcerations (Stage 2). Stage 3 would be charachterized by severe symptoms consisting of diarrhea, emaciation, pustules, necrosis, dyspnea, and delirium. Stage 4 for the surviving cohort is characterized as the chronic form of glanders, with protracted periods of illness (similar to Stage 2) interrupted by periods of acute disease (similar to Stage 3). The non-surviving cohort dies at the end of Stage 3.

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[111] Anno et al., *AMedP-8 (Biological) Methods Report*, 50.

[112] Gregory and Waag, "Glanders," in *Medical Aspects of Biological Warfare*, 131.

Table 23. Illness Profile for Glanders

	Stage 1	Stage 2	Stage 3	Stage 4 (survivors)
Signs and Symptoms (S/S)	Localized pain and inflammation, fever, swelling, chills, and phlegmon	Cough, suppuration, red streaks, papular eruption nasal discharge, abscess, pain, and ulcerations	Diarrhea, emaciation, pustules, necrosis, dyspnea, and delirium	Chronic glanders
S/S Severity	Severity Level 1 ("Mild")	Severity Level 2 ("Moderate")	Severity Level 3 ("Severe")	Severity Level 2 ("Moderate")
Outlook	Individual will progress to Stage 2.	Individual will progress to Stage 3.	Individual will progress to Stage 4.	Individual will likely recover after a prolonged illness.

G. Duration of Illness

Medical Aspects of Biological Warfare estimates the duration of illness to range from a few days to weeks or months or years.[113] The *AMedP-8 (Biological) Methods Report* estimates several duration ranges. The acute form of glanders was estimated to last 10 to 30 days with an average of 19 days, and chronic glanders was roughly estimated to last months to years.[114]

The duration values were compared to all case reports regardless of clinical forms, excluding cases that were incomplete. Using the duration of incomplete cases would shorten the illness duration. To generate an average duration of illness, 181 cases were used. The untreated duration used 174 cases, and the treated duration used 7 cases. Table 24 represents the duration of the illness according to the data collected.

[113] Gregory and Waag, "Glanders," in *Medical Aspects of Biological Warfare*.

[114] Anno et al., *AMedP-8 (Biological) Methods Report*, 213.

Table 24. Average Glanders Duration of Illness

Type of Duration	Duration
Overall (181 cases)	364 days
Untreated (174 cases)	370 days
Treated (7 cases)	28 days

The calculated overall and untreated durations were significantly longer than any previously determined illness duration. This is because in calculating these values the clinical forms were not separated and calculated separately. Robins explains that there is no distinct duration gap between acute and chronic clinical forms. One way to attempt to distinguish between acute and chronic is to choose a reasonable set number and assume that anything shorter is acute and anything longer is chronic. Robins suggested a set duration value of six weeks for acute cases. [115]

Following Robins' demarcation of six weeks as defining the acute form of glanders, all the data with duration less than six weeks was then analyzed to estimate a distribution function for the duration of illness. Using the @RISK software tool, a Weibull function was fitted to the plotted data with shape parameter value of 1.90 and a scale parameter value of 26.0, providing a mean duration of 23.1 days and a standard deviation of 12.7 days. The CDF for the proposed glanders duration of illness submodel is:

$$F(t) = 1 - e^{-(t/\beta)^{\alpha}}$$

where:

F is the cumulative fraction of persons with glanders who have completed the course of disease,

t is the duration [weeks],

α is the shape parameter [= 1.90], and

β is the scale parameter [= 26.0].

The Weibull CDF and underlying data are illustrated in Figure 8.

[115] Robins, *A Study of Chronic Glanders in Man with Report of a Case Analysis of 156 Cases Collected from the Literature and an Appendix of the Incidence of Equine and Human Glanders in Canada*.

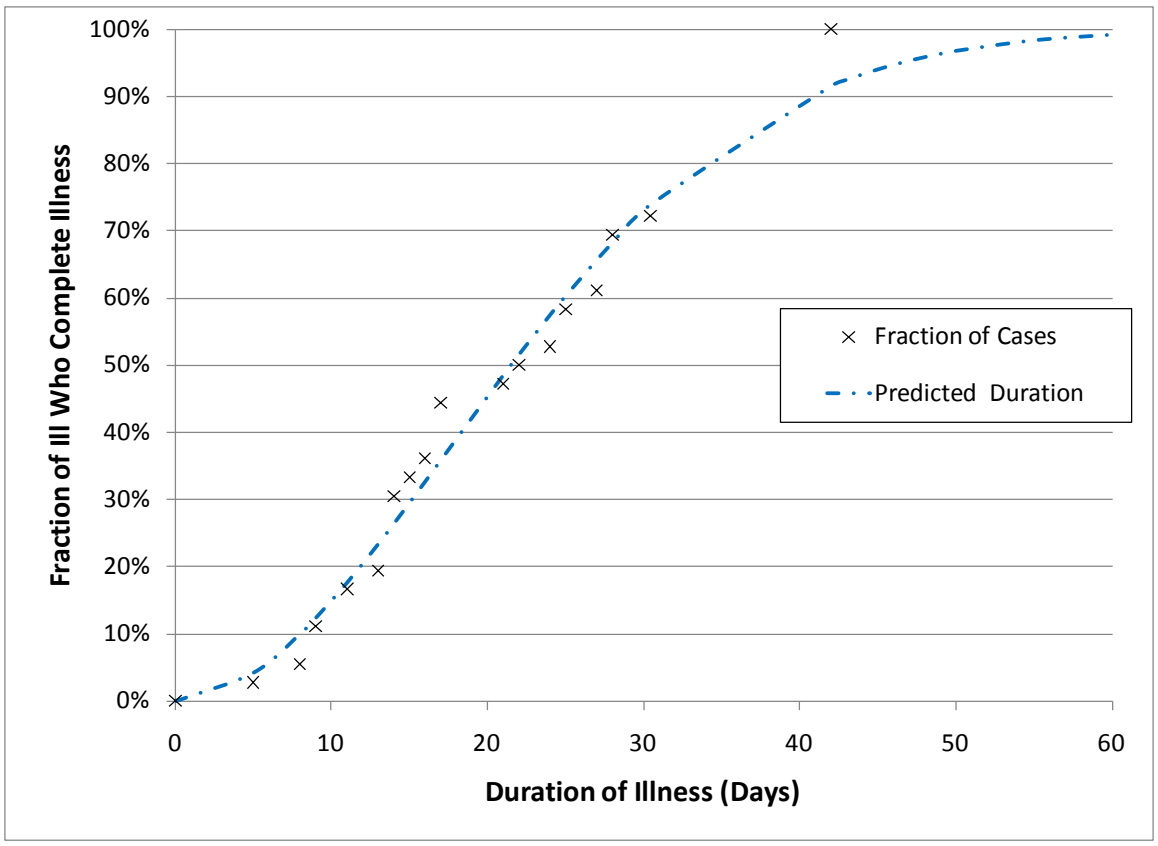

Figure 8. Cumulative Distribution of Glanders Duration of Illness

The duration of individual stages of glanders are not well described in the case studies, although the *AMedP-8 (Biological) Methods Report* has a very interesting analysis of ten cases.[116] Roughly equating their "Severity 1" period to Stage 1, "Severity 2" to Stage 2, and "Severity 3" and "Severity 4" to Stage 3, then the duration of each stage is proposed as a fraction of the total duration. This would set the duration of Stage 1 as 30% of the total duration, Stage 2 as 45% of the total, and Stage 3 as (the remaining) 25%.

H. Medical Countermeasures and Treatment

Little research has been done to determine treatments and countermeasures because of the scarcity of glanders in the modern world. The *AMedP-8 (Biological) Methods Report* report states that sulfadiazine, ciprofloxacin and other similar medicines could potentially cure glanders.[117] *Medical Aspects of Biological Warfare* found that quite a few drugs could possibly cure a glanders infection. These drugs are: amikacin, netilmicin,

[116] Anno et al., *AMedP-8 (Biological) Methods Report*, 50–52.

[117] Anno et al., *AMedP-8 (Biological) Methods Report*.

gentamicin, streptomycin, tobramycin, azithromycin, novobiocin, piperacillin, imipenem, ceftazidime, tetracycline, oxytetracycline, minocyclin, doxycycline, ciprofloxacin, norfloxacin, ofloxacin, erythromycin, sulfadiazine, and amoxicillin-clavulanate.[118]

In 1946, Howe reported that six individuals exposed to glanders were all treated with sulfadiazine. All six individuals survived and made a full recovery.[119] In 2001, Srinivasan et al. reports that an individual was exposed to glanders and was treated with imipenem and doxycycline. Two weeks later, the treatment regimen changed to doxycycline and azithromycin. From the recent 2001 exposure, tests were taken and found that glanders had an initial sensitivity to imipenem, ceftazidime, and tetracycline.[120] From the collected data, it appears that sulfadiazine is the best cure for a glanders infection because it has been demonstrated efficacious in six out of the six cases. For other possible treatments, more research needs to be conducted to prove efficacy in curing glanders. Srinivasan states that "there are few data regarding the antibiotic treatment of glanders, since the disease had largely disappeared by the time antibiotics became available. However, treatment of the disease in the setting of bioterrorism may be more difficult if the organism is drug resistant."[121]

I. Summary and Conclusions

As with brucellosis, the parameters described in this chapter were derived from a collection of articles which range from century old collection of case studies to microbiological studies from the past decade. What they are not derived from are controlled animal exposure experiments which quantify the parameters of interest. It is the recommendation of the authors to use the parameters described in this chapter, but to simultaneously pursue a research program to quantitatively characterize the infectivity, lethality, incubation, duration and course of illness of glanders. Until such time as this research program is practical, it is further recommended that a more thorough comparison of glanders be made with other similar diseases (such as melioidosis) to derive the most appropriate functions for the human response parameters of interest. Based on the available data, analysis, and literature review as described in the preceding sections, the authors recommend using the parameter values provided in Table 25 to model glanders in humans. The illness profile for glanders, provided in Section F, is repeated in Table 26.

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[118] Gregory and Waag, "Glanders," in *Medical Aspects of Biological Warfare*.

[119] Calderon Howe and Winston Miller, "Human Glanders: Report of Six Cases," *Annals of Internal Medicine* 26, no. 1 (1947): 93–115.

[120] Arjun Srinivasan et al., "Glanders in a Military Research Microbiologist," *The New England Journal of Medicine* 345 (2001): 256–58.

[121] Ibid.

Table 25. Glanders Model Parameters Summary Table

Submodel	Type	Parameters
Infectivity	Lognormal distribution	ID_{50} = 24.5 CFU Probit slope = 1.93 probits/log(dose)
Lethality	Case fatality rate	70%
Incubation period	Lognormal distribution	Mean = 8.29 days Standard deviation = 13.0 days
Duration of illness	Weibull function	α = 1.90, β = 26.0
• Stage 1	Rate	30% of total duration
• Stage 2	Rate	45% of total duration
• Stage 3	Rate	25% of total duration

Table 26. Illness Profile for Glanders

	Stage 1	Stage 2	Stage 3	Stage 4 (survivors)	Stage 4 (non-survivors)
Signs and Symptoms (S/S)	Localized pain and inflammation, fever, swelling, chills, and phlegmon	Cough, suppuration, red streaks, papular eruption nasal discharge, abscess, pain, and ulcerations	Diarrhea, emaciation, pustules, necrosis, dyspnea, and delirium	Chronic glanders	None (Dead)
S/S Severity	Severity Level 1 (“Mild”)	Severity Level 2 (“Moderate”)	Severity Level 3 (“Severe”)	Severity Level 2 (“Moderate”)	
Outlook	Individual will progress to Stage 2	Individual will progress to Stage 3	Individual will progress to Stage 4	Individual will likely recover after a prolonged illness	Death

4. Q Fever

This chapter presents the proposed human response model parameter values for Q fever, the third of five agents discussed in this document. It describes the results of the literature review and data analyses conducted by the IDA study team in the acquisition and derivation of these values.

A. Introduction

Q fever is caused by the Gram-negative bacterium *Coxiella burnetii* in the tribe *Rickettsiae*.[122] Q fever is a zoonotic disease, and person-to-person transmission is very rare.[123] The primary animal reservoirs for Q fever are cattle, sheep, and goats. Ticks can also carry the disease, although they are more able to infect animals than humans.[124]Animals, however, do not often show symptoms from the infection, except for an occasional increase in abortions.[125] Humans are generally infected by inhaling the organisms let into the air from handling infected animals or their byproducts. *Coxiella burnetii* can survive for several weeks in areas where animals used to be located and can also travel long distances through the air.[126] Therefore, some people can become infected in a city where they do not interact with animals just because of the infectivity and wide dispersal range of the organism.[127] Because it is so hardy when aerosolized, it has been listed as a potential bioweapon. It may not be as good a candidate as other agents, however, because it has a lower mortality, has a longer incubation time, and is characterized by a milder illness than other agents.[128]

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[122] Leigh A. Sawyer, Daniel B. Fishbein, and Joseph E. McDade, "Q fever: Current Concepts," *Reviews of Infectious Disease*s 9, no. 5 (September–October 1987): 935–46.

[123] W. D. Tigertt, A.S. Benenson, and W.S. Gochenour, "Airborne Q Fever," *Microbiology and Molecular Biology Reviews* 25 (September 1961): 285–93.

[124] Sawyer, Fishbein, and McDade, "Q Fever: Current Concepts."

[125] P. A. Bossi et al., "Bichat Guidelines for the Clinical Management of Q Fever and Bioterrorism-Related Q Fever," *Eurosurveillance* 9, no. 12 (2004): 1–5.

[126] M. Maurin and D. Raoult, "Q Fever," *Clinical Microbiology Reviews* 12, no. 4 (October 1999): 518–33.

[127] U. Terheggen and P.A. Leggat. "Clinical Manifestations of Q Fever in Adults and Children," *Travel Medicine and Infectious Disease* 5 (2007): 159–64.

[128] Bossi et al., "Bichat Guidelines for the Clinical Management of Q Fever and Bioterrorism-Related Q Fever."

B. Primary References and Data Sets

As shown in Table 3, the authors relied on three of the four "capstone" documents for development of the Q fever human response model: *Medical Aspects of Biological Warfare*,[129] the *AMedP-8 (Biological) Methods Report*, and *Consequence Analytic Tools for NBC Operations*.

The latter two documents describe work conducted by the Pacific Sierra Research Corporation (PSR) in support of earlier versions of AMedP-8. Specifically, PSR developed a stochastic, dose-dependent model of performance over time for individuals ill with Q fever; this model was derived from experimental data recorded during a series of human and animal tests conducted by W. D. Tigertt and colleagues. In the development of the Q fever human response model described in this chapter, the authors relied heavily on the documentation of Tigertt's tests, provided in:

- Tigertt, W.D., "Studies on Q Fever in Man." In J.E. Smadel (ed.), *Symposium on Q Fever* (Washington, DC: Army Medical Service Graduate School, Walter Reed Army Medical Center, Government Printing Office, 1959).
- Tigertt, W.D. and A.S. Benenson, "Studies on Q Fever in Man." *Transactions of the Association of American Physicians* 69 (1956): 98-104.
- Tigertt, W.D., A.S. Benenson, and W.S. Gochenour. "Airborne Q Fever." *Microbiology and Molecular Biology Reviews* 25 (September 1961): 285-93.

C. Infectivity

Q fever is highly infectious and even a single organism may be sufficient to cause an infection.[130] Most reports in the literature give infective doses of between one and ten organisms.[131] *Medical Aspects of Biological Warfare* states that a single microorganism can cause an infection, although it does not give specific infective dose values.[132] In a study designed to establish the infectivity of Q fever in humans, Tigertt, Benenson, and Gochenour[133] exposed guinea pig and human subjects (MRVs) to aerosol concentrations

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[129] David M. Waag, "Q Fever," in *Medical Aspects of Biological Warfare*, 199–213.

[130] Sawyer, Fishbein, and McDade, "Q Fever: Current Concepts."

[131] See, for example, Bossi et al., "Bichat Guidelines for the Clinical Management of Q Fever and Bioterrorism-Related Q Fever," and J. D. Hartzell et al., "Q Fever: Epidemiology, Diagnosis, and Treatment." *Mayo Clinic Proceedings* 83, no. 5 (May 2008): 574–9, both of which state that infection can be caused by one to five organisms; similarly, in K. E. Russell-Lodrigue et al., "*Coxiella burnetii* Isolates Cause Genogroup-Specific Virulence in Mouse and Guinea Pig Models of Acute Q Fever," *Infection and Immunity* 77, no. 12 (December 2009): 5640–50, the authors note that infection can be caused by as few as ten organisms.

[132] Waag, "Q Fever" In *Textbooks of Military Medicine: Medical Aspects of Biological Warfare*, 199–213.

[133] Tigertt, Benenson and Gochenour, "Airborne Q Fever."

of *Coxiella burnetii*. The subjects were exposed for one minute to aerosol clouds created from various dilutions of a slurry containing approximately 20 billion infectious particles per milliliter. As shown in Table 27, Tigertt, Benenson, and Gochenour originally described the concentration of agent in terms of the slurry dilution (infectious particles per total slurry particles). However, these studies also determined the median guinea pig infective dose via injection ($GPIPD_{50}$), and this dose unit served as the unit of measure for Q fever doses expressed in the subsequent article written by Tigertt.[134] Infection in guinea pigs was determined through serologic studies; infection in man was determined through serological studies and an onset of clinical symptoms consistent with Q fever, specifically a sustained fever in excess of 100ºF.

Tigertt, Berenson and Gochenour stated that infection in guinea pigs could be initiated by one organism, but they did not specify how this number was determined from the data provided. Another study by Ormsbee, et al.[135] examined the median infective doses of a variety of rickettsial diseases, and found it to be two organisms for guinea pigs given Q fever via injection. For the purposes of IDA's research, the human data from Tigertt's study was compiled and the conversion factor of two organisms per $GPIPD_{50}$ given by Ormsbee, et al. was then used to determine the number of organisms associated with such a dose. The human infection data is given in Table 27.

Table 27. Human Q Fever Infection Data from Tigertt Studies

Slurry Dilution	Equivalent $GPIPD_{50}$s	Organisms	Humans Exposed	Humans Infected	% Infected
10^{-6}	1	2	2	0	0%
10^{-5}	10	20	5	2	40%
$10^{-4.5}$	50	100	3	3	100%
10^{-4}	150	300	8	7	87.5%
10^{-3}	1,500	3,000	5	4	80%
10^{-2}	15,000	30,000	4	4	100%
10^{-1}	150,000	300,000	2	2	100%

Using the maximum likelihood dose response calculation method described by Tallarida,[136] the authors were able to derive an ID_{50} of 26 organisms and probit slope of 0.776 from the Tigertt data.

[134] Tigertt, "Studies on Q Fever in Man," 39–46.

[135] R. M. Ormsbee et al., "Limits of Rickettsial Infectivity," *Infection and Immunity* 19, no. 1 (January 1978): 239–45.

[136] Tallarida, "Quantal Dose-Response Data: Probit and Logit Analysis."

These values are very similar to the ID_{50} of 30 organisms and probit slope of 0.779 probits per logarithm of dose given in the *AMedP-8 (Biological) Methods Report*,[137] derived from 42 MRV cases. These 42 cases include the 29 cases described by Tigertt and provided in Table 27, as well as 13 additional unpublished clinical cases.[138] The data used to calculate infectivity in the *AMedP-8 (Biological) Methods Report* are provided in Table 28. Note that the dose data contained in that document are expressed in units of $GPIPD_{50}$; in Table 28 they have been converted to organisms using the ratio of two organisms per $GPIPD_{50}$ described by Ormsbee.[139] Note also that the *AMedP-8 (Biological) Methods Report* data includes 4 cases exposed to 47 $GPIPD_{50}$s (94 organisms), and none exposed to 50 $GPIPD_{50}$s (100 organisms). Since the Tigertt studies describe 3 cases exposed to 50 $GPIPD_{50}$s, and since these cases are presumably represented in the *AMedP-8 (Biological) Methods Report* data set, it must be presumed that the authors of that report modified the Tigertt dose data upon further review of the unpublished MRV data and clinical case reports.

Table 28. Human Q Fever Infectivity Data used in *AMedP-8 (Biological) Methods Report*

Dose (Organisms)	Number Exposed	Number Infected	Percent Infected
2	2	0	0%
20	5	2	40%
94	4	3	75%
300	8	7	88%
3,000	5	5	100%
7,274 to 7,760	8	7	88%
30,000	4	4	100%
47,400 to 51,058	4	4	100%
300,000	2	2	100%

Using the Tallarida method,[140] the authors were able to derive an ID_{50} of 30 organisms and probit slope of 0.782 probits per logarithm of dose from the *AMedP-8 (Biological) Methods Report* data set. This ID_{50} matches that proposed in the *AMedP-8 (Biological) Methods Report* and the probit slope is nearly identical. Pending access to the unpublished case data and assuming that these data will match those described in the *AMedP-8 (Biological) Methods Report* and shown in Table 28, the authors recommend modeling Q fever infectivity from the *AMedP-8 (Biological) Methods Report* data set: as

[137] Anno et al., *AMedP-8 (Biological) Methods Report*, 126.

[138] Anno et al., *AMedP-8 (Biological) Methods Report*, 125.

[139] Ormsbee et al., "Limits of Rickettsial Infectivity."

[140] Tallarida, "Quantal Dose-Response Data: Probit and Logit Analysis."

a lognormal distribution with an ID_{50} of 30 organisms and a probit slope of 0.782 probits per logarithm of dose. This distribution has a mean of 3.40 and standard deviation of 3.59.

The CDF of the lognormal distribution that corresponds to these data and used to model the aerosol infectivity of Q fever in humans is:

$$F(d) = \frac{1}{2} + \frac{1}{2}\text{erf}\left[\frac{\ln(d) - \mu}{\sigma\sqrt{2}}\right]$$

where:

F is the cumulative fraction of persons who have become infected with Q fever,

d is the infective dose [organisms],

μ is the mean of the variable's natural logarithm [= $\ln(ID_{50})$ = ln(30 organisms) =3.40],

m is the probit slope [= 0.782 probits/log(dose)],

σ is the standard deviation of the variable's natural logarithm [= $e^{1/m}$ = $e^{1/0.782}$ = 3.59], and

erf is the error function where $\text{erf}(x) = \frac{2}{\sqrt{\pi}}\int_0^x e^{-t^2}\,dt$.

The proposed Q fever infectivity model is shown graphically in Figure 9, together with the underlying data.

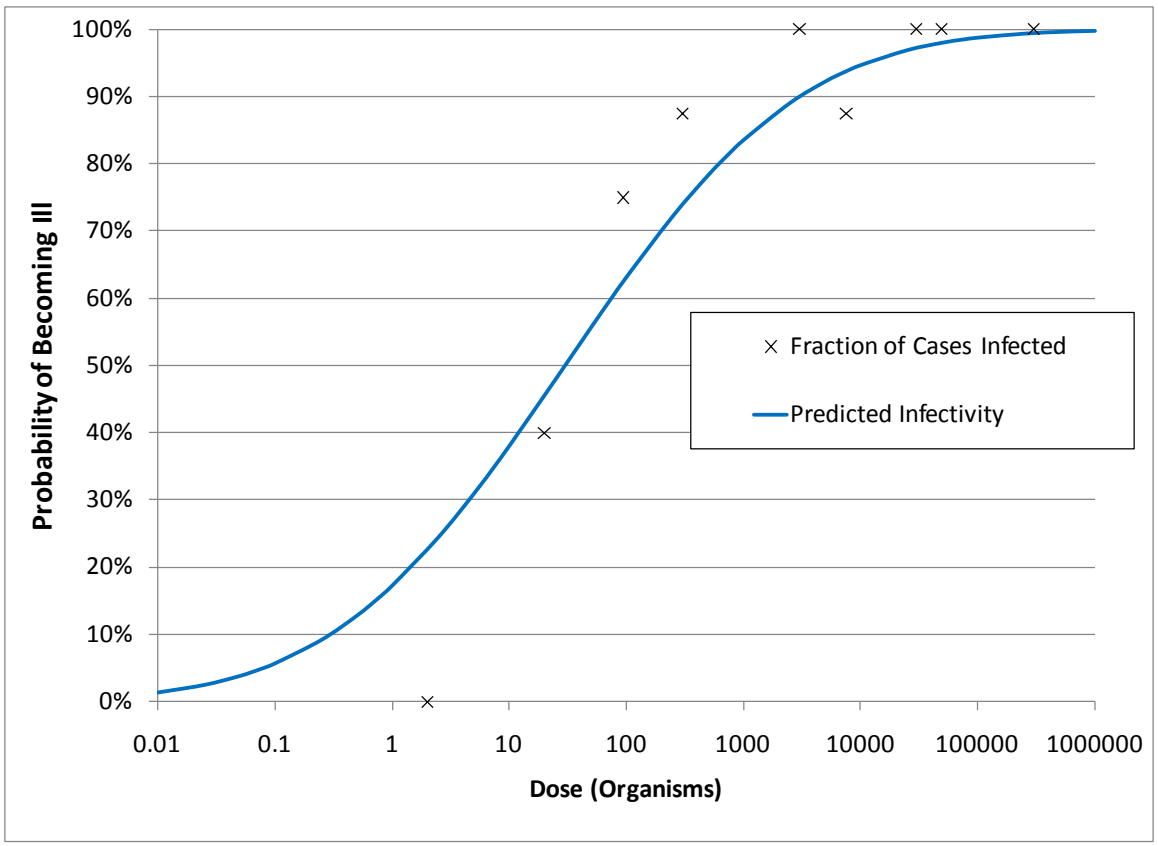

Figure 9. Dose-Related Probability of Q Fever Infection

D. Lethality

Death from acute Q fever is very rare. *Medical Aspects of Biological Warfare* states that less than 1 % of patients will die from the disease,[141] while the *AMedP-8 (Biological) Methods Report* did not give information about lethality and assumed that all Q fever patients would recover, even in the absence of treatment.

In their 1999 review of "recently reported epidemiological situations"—outbreaks of Q fever involving several hundred patients throughout the world—Maurin and Raoult found that 1% to 2% of patients died.[142] The percentage of these cases that were treated with antibiotics is unknown. Since Q fever was initially described around the start of the antibiotic era, there are few clinical studies of acute Q fever that did not consider the effects of treatment. In Hornibrook's 1940 study,[143] involving a small number of cases, 1

[141] Waag, "Q Fever" In *Textbooks of Military Medicine: Medical Aspects of Biological Warfare*, 202.

[142] Maurin and Raoult, "Q Fever," 533.

[143] J. W. Hornibrook and K.R. Nelson, "An Institutional Outbreak of Pneumonitis I. Epidemiological and Clinical Studies," *Public Health Reports* 55, no. 43 (October 25, 1940): 1936–44.

out of 15 patients died (6.7%). In Derrick's original 1944 study, 3 of 176 untreated cases died (1.7%),[144] and in a later study that considered much of the same data, 4 of 273 untreated cases died (1.5%).[145]

In cases of chronic Q fever—about 2% of the total reported Q fever infections—death is much more common.[146] In particular, endocarditis is very common in such cases, occurring 60 to 70% of the time, and left untreated has a lethality rate estimated to be as high as 60%.[147]

Even considering chronic cases, the overall lethality rate for diagnosed cases of untreated Q fever is somewhere between 1% and 2%. Because Q fever is assumed to be widely underreported, the true lethality rate is likely even lower. Maurin and Raoult, for example, noted that in many nations Q fever is not a reportable disease, and in many others it is often unreported because the required diagnostic tests are not readily available and confirmatory diagnoses cannot be made.[148] Consequently, for purposes of modeling human response, the authors found the lethality rate to be negligible and did not consider it further.

E. Incubation Period

The incubation period for Q fever generally lasts a few weeks, although this can depend upon the dose. *Medical Aspects of Biological Warfare* gave an incubation period of between a few days and several weeks. Various clinical case studies of naturally occurring outbreaks provide incubation periods ranging from a few days to a few weeks. For example, in Huebner's study of an outbreak at the National Institutes of Health, the incubation period ranged from thirteen to eighteen days.[149] In Spelman's study of serological cases from a hospital, 4 had identified incubation periods of 21, 28, 35, and 39 days.[150] Marrie's study gave different incubation periods for 13 outbreaks,

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[144] E. H. Derrick, "The Epidemiology of Q Fever," *The Journal of Hygiene* 43, no. 5 (April 1944): 357–61.

[145] E. H. Derrick, "The Course of Infection with *Coxiella burneti*," *The Medical Journal of Australia* 1, no. 21 (May 26, 1973): 1051–7.

[146] Sawyer, Fishbein, and McDade, "Q Fever: Current Concepts."

[147] D. Raoult et al., "Treatment of Q Fever Endocarditis," *Archives of Internal Medicine* 159 (January 25, 1999): 167–73.

[148] Maurin and Raoult, "Q Fever," 532–535.

[149] R. J. Huebner, "Report of an Outbreak of Q Fever at the National Institute of Health," *American Journal of Public Health* 37 (April 1947): 431–40.

[150] Denis W. Spelman, "Q Fever: A Study of 111 Consecutive Cases," *The Medical Journal of Australia* 1, no. 13 (June 26, 1982): 547–53.

constituting 51 total cases, all due to parturient cats.[151] These incubation periods ranged from 4 to 30 days, with most cases occurring about 14 days after exposure.

The incubation period given by the *AMedP-8 (Biological) Methods Report* was derived from a combination of the dose dependent time to onset recorded in the Tigertt studies[152] and the unpublished case studies described in the infectivity submodel section above. The authors found a good correlation between the logarithm of dose and the time to onset, of the form:

$$t_0 = \alpha + \beta * \log(N_0)$$

where:

t_0 = time to onset (days), and

N_0 = dose ($GPIPD_{50}$s).[153]

From the body temperature measurements contained in the clinical records associated with the Tigertt study subjects and the unpublished MRV cases, the *AMedP-8 (Biological) Methods Report* provided values for the α and β parameters, equal to 17.3425 and -1.8162, respectively. The function for time to onset thus reported was:

$$t_0 = 17.3425 - 1.8162 * \log(GPIPD_{50})$$ [154]

Neither the *AMedP-8 (Biological) Methods Report* nor the earlier *Consequence Analytic Tools for NBC Operations* provide the time to onset data for the unpublished MRV cases. The time to onset data published by Tigertt and Benenson and presumably used in the *AMedP-8 (Biological) Methods Report* are presented in Table 29.

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[151] T. J. Marrie et al., "Exposure to Parturient Cats: A Risk Factor for Acquisition of Q Fever in Maritime Canada," *The Journal of Infectious Diseases* 158, no. 1 (July 1988): 101–8.

[152] Tigertt and Benenson, "Studies on Q Fever in Man."

[153] Anno et al., *AMedP-8 (Biological) Methods Report*, 130.

[154] Ibid., 129.

An evaluation of the dose data in Table 29 using the function described by the *AMedP-8 (Biological) Methods Report* provides a set of predicted times of onset that are a relatively poor fit to the observed onset times, being consistently shorter than those observed. On the other hand, the authors were able to derive parameter values for the same function using the Tigertt onset data alone that provided a better fit to the observed onset times.[155] The equation for this function is:

$$t_0 = 19.647 - 1.8808 \log(N_0)$$

where:

t_0 is the incubation period (days), and

N_0 is dose (organisms).

The times to onset given dose predicted by both the *AMedP-8 (Biological) Methods Report* function and those predicted by the authors are provided in Table 29.

[155] The onset times predicted by the *AMedP-8 (Biological) Methods Report* for the Tigertt data set had an R^2 value of 0.40 when compared with the observed data; those predicted by the function derived by the authors had an R^2 value of 0.73.

Table 29. Q Fever Observed and Predicted Incubation Period Data

$GPIPD_{50}$	Organisms	Observed Time to Onset (days)	*AMedP-8 (Biological) Methods Report* Predicted Time to Onset (days)	IDA Predicted Time to Onset (days)
10	20	17	16	17
10	20	17	16	17
50	100	14	14	16
50	100	17	14	16
50	100	17	14	16
150	300	12	13	15
150	300	14	13	15
150	300	15	13	15
150	300	15	13	15
150	300	16	13	15
150	300	18	13	15
1,500	3,000	13	12	13
1,500	3,000	13	12	13
1,500	3,000	14	12	13
1,500	3,000	14	12	13
15,000	30,000	9	10	11
15,000	30,000	9	10	11
15,000	30,000	11	10	11
15,000	30,000	13	10	11
150,000	300,000	10	8	9
150,000	300,000	10	8	9

From a comparison of the Tigertt dose data presented in Table 29 and the infectivity dose data used in the *AMedP-8 (Biological) Methods Report* and presented in Table 28, the unpublished MRV case subjects were apparently exposed to doses of 47 $GPIPD_{50}$s, 3,637 to 3,880 $GPIPD_{50}$s, and 23,700 to 25,529 $GPIPD_{50}$s. These doses—13 in all—were well within the dose range of 1 to 150,000 $GPIPD_{50}$s used in the Tigertt studies, and presumably would not have been associated with onset times significantly different than those observed by Tigertt. In the absence of these data, however, it is difficult to determine the reasons for the differences between the time to onset parameter values given in the *AMedP-8 (Biological) Methods Report* and those derived by the authors herein.

Until the MRV records can be reviewed, the authors recommend using time to onset parameters they derived from the Tigertt data set alone, as described above. These are portrayed graphically in Figure 10.

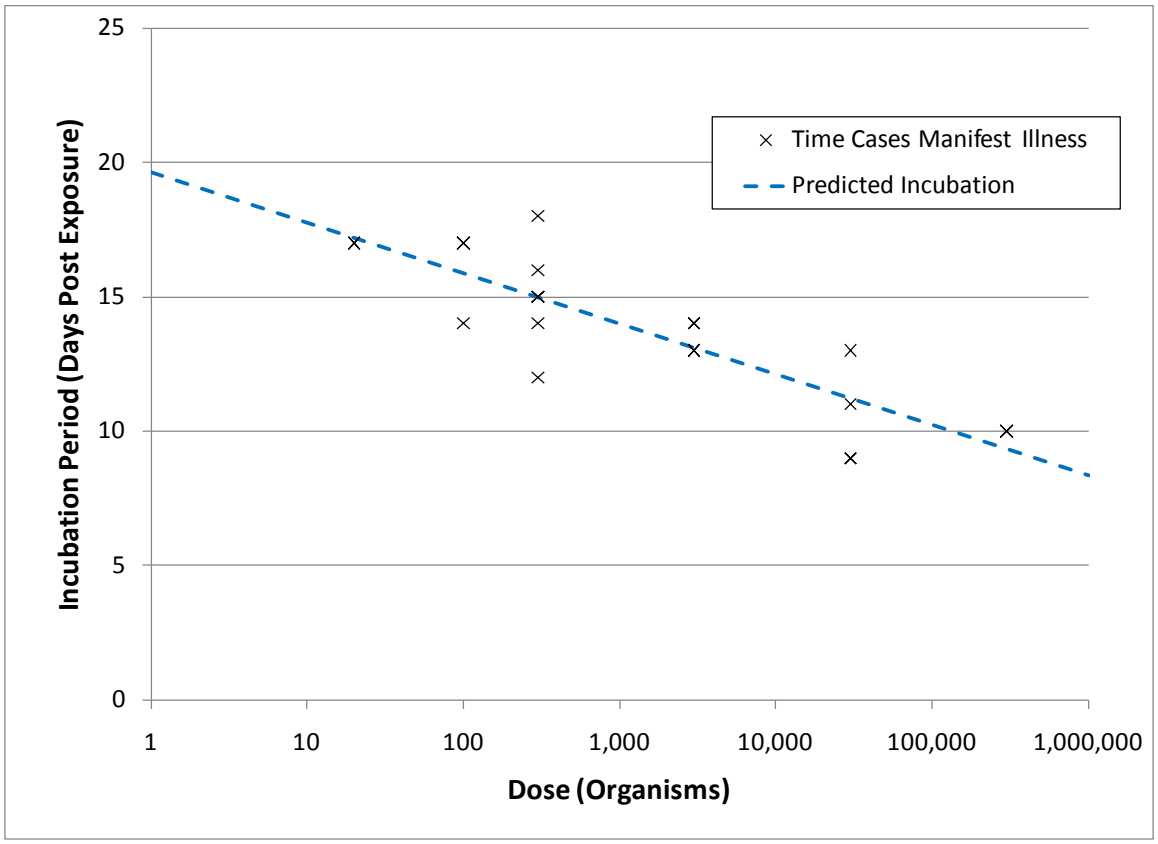

Figure 10. Q Fever Incubation Period

F. Illness Profile

Q fever is a relatively mild, febrile illness that rarely requires hospitalization. Maurin and Raoult report that 95% of symptomatic patients will not require hospitalization.[156] Delsing speculates that only 20% of Q fever infections require medical attention and that only 2–3% result in hospitalization.[157]

Many individuals infected with Q fever do not become ill; Bossi, for example, estimates that 50% of cases are asymptomatic, while Maurin and Raoult estimate that 60% are asymptomatic.[158] When symptoms do occur, they are varied and non-specific. *Medical Aspects of Biological Warfare*[159] describes the most common symptoms of Q

[156] Maurin and Raoult, "Q Fever."

[157] Delsing, C.E. and B.J. Kullberg. "Q fever in the Netherlands: a concise overview and implications of the largest ongoing outbreak." *The Netherlands Journal of Medicine* 66, no. 9 (October 2008): 365–7.

[158] See Bossi et al., "Bichat Guidelines for the Clinical Management of Q Fever and Bioterrorism-Related Q Fever," and Maurin and Raoult, "Q Fever."

[159] Waag, "Q Fever," in *Medical Aspects of Biological Warfare*, 203.

fever as fever, severe headache, and chills, with fatigue and sweats frequently found. Other symptoms occasionally associated with Q fever include cough, nausea, vomiting myalgia, arthralgia, and chest pain. Pneumonia is common, particularly in cases where infection occurs through inhalation, and hepatitis is often found. Interestingly, the rates of pneumonia and hepatitis in outbreaks of Q fever are highly variable and appear to be influenced by geography. In a study of 66 hospitalized cases of Q fever in the province of Barcelona in Spain, 37 (56%) had pneumonia and 22 (33%) had hepatitis.[160] This fits with another study in the Basque area of Spain (Valmaseda), in which 25 out of 42 patients (59.5%) had respiratory symptoms, or pneumonia, and 16 out of 42 (38.1%) had liver involvement, or hepatitis.[161] Other parts of Spain, however, appear to have different rates, since in Sevilla, in the south of Spain, 148 out of 231 patients (64%) had hepatitis while only 41 out of 231 patients (17.7%) had respiratory symptoms.[162] Since these latter were cases from a hospital, however, the severity was possibly skewed.

The variability in presentation of illness may result from differences in source, route of entry, dose, or virulence of the organism.[163] Maurin and Raoult speculate that the differences may be due to route of entry (whether aerosol or ingestion), but this is still not well understood.[164] The pneumonia is usually atypical and often only diagnosed via an X-ray, with a very low incidence of acute respiratory distress.[165] Similarly, hepatitis is usually shown through abnormal liver function tests, rather than actual jaundice.

Some articles give specific outlines for the course of the illness. This does not change the symptom severity profile, however, since all parts of the illness appear to fall under the same severity scale of "moderate." Derrick's original characterization of the disease[166] described an acute onset with malaise, anorexia, headache, pains in the back and limbs, and feverishness. As the illness progresses, the symptoms became more severe as temperature increased, up to about 40°C (104°F). Headache was persistent and often interfered with sleep. The symptoms abated as body temperature fell.

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[160] M. Sampere et al., "Q Fever in Adults: Review of 66 Cases," *European Journal of Clinical Microbiology & Infectious Diseases* 22 (2003): 108–10.

[161] C. A. Errasti et al., "An Outbreak of Q Fever in the Basque Country," *The Canadian Medical Association Journal* 131 (July 1, 1984): 48–9.

[162] A. de Alarcon et al., "Q Fever: Epidemiology, Clinical Features and Prognosis: A Study from 1983 to 1999 in the South of Spain," *Journal of Infection* 47 (2003): 110–6.

[163] Sawyer, Fishbein, and McDade, "Q Fever: Current Concepts."

[164] Maurin and Raoult, "Q Fever."

[165] Ibid.

[166] E. H. Derrick, "Q Fever, a New Fever Entity: Clinical Features, Diagnosis and Laboratory Investigation," *Reviews of Infectious Diseases* 5, no. 4 (July–August 1983): 790–800.

Derrick's later characterization of the illness also described the usual course of fever.[167] Typically, there would be a rapid ascent of fever for two to four days, with a plateau at about 102–104°F (39–40°C), sometimes broken by remissions. There would be a defervescence and an overall duration of five to fourteen days. Twenty eight percent of the fevers came twice. In some, the fever was high for a variable length of time and the temperature fell gradually. Maurin and Raoult[168] describe the same course of illness, referencing Derrick. Baca and Paretsky[169] also describe a similar profile, with a febrile onset reaching a plateau of 40°C (104°F) within two to four days, later accompanied by malaise, anorexia, muscle pain, weakness, and intense headache. Later, the headache became generalized and continued in intensity throughout the disease. A gradual defervescence would then occur over a one to two week period, although in older patients the fever may last longer and may display biphasic peaks.

In the clinical studies reviewed by the authors, symptoms that were reported in more than 50% of cases are included in the Q fever illness profile, shown inTable 30; these are fever, chills, headache, myalgia, pneumonia, and hepatitis. As discussed in Section G, the severity of Q fever symptoms does not appear to change over time. Consequently, the illness profile for Q fever contains only a single stage.

Table 30. Q Fever Illness Profile

	Stage 1
Signs and Symptoms (S/S)	Fever, chills, headache, myalgia Pneumonia; hepatitis
S/S Severity	2 (Moderate)
Outlook	Patient is likely to recover

G. Duration of Illness

The duration of Q fever is generally cited to be between one and three weeks. *Medical Aspects of Biological Warfare* cites a duration of approximately 13 days.[170] The *AMedP-8 (Biological) Methods Report* cites a duration of 3 to 7 days with antibiotic

[167] Derrick, E.H., "The Course of Infection with *Coxiella burneti*."

[168] Maurin and Raoult, "Q Fever."

[169] O. G. Baca and D. Paretsky, "Q Fever and *Coxiella burnetii*: A Model for Host-Parasite Interactions," *Microbiological Reviews* 47, no. 2 (June 1983): 127–49.

[170] Waag, "Q Fever," in *Medical Aspects of Biological Warfare*, 203.

given within the first three days of symptoms or a duration of 6 to 14 days without treatment. The model used was

$$Duration(days) = 3.6924 + 0.2741 * \log(dose).$$

The *AMedP-8 (Biological) Methods Report* derived duration from the various Tigertt studies. Although Tigertt provided data on treated patients, the *AMedP-8 (Biological) Methods Report* corrected for this by assuming that the duration of untreated Q fever was probably twice the treated duration.[171] This assumption was based on two studies of the effect of treatment on the course of Q fever. A review of the supporting references suggests that while antibiotics can be effective in shortening the course of the disease, the 50% observed reduction was specifically associated with fever.[172] Other symptoms, such as lethargy, sweats, and headache, persisted for days or weeks, and the relationship between antibiotic use and persistence of these symptoms was not described. Since the Q fever model described in the *AMedP-8 (Biological) Methods Report* was based on fever, this assumption was more appropriate there than in the present case, where duration and severity of all symptoms are considered.

Two published studies provided data on the duration of untreated Q fever: Derrick's study, which described duration in 138 cases of untreated Q fever in Australia,[173] and Hornibrook's study, which described specific duration in 13 cases.[174] The duration data compiled from these two studies are shown in Table 31, and as discussed below, was used to develop the model for duration of illness for untreated Q fever.

[171] Anno et al., *AMedP-8 (Biological) Methods Report*, 132.

[172] Spelman, "Q Fever: A Study of 111 Consecutive Cases," 551, and Sawyer, Fishbein, and McDade, "Q Fever: Current Concepts," 940.

[173] Derrick, "The Course of Infection with *Coxiella burneti*."

[174] Hornibrook and Nelson, "An Institutional Outbreak of Pneumonitis I. Epidemiological and Clinical Studies."Hornibrook's data set included two other cases in which duration of illness was described generally as "more than five days;" these were disregarded from the data used in this study.

Table 31. Duration Data from Derrick[31] & Hornibrook[33]

Febrile Duration	Derrick Frequency	Hornibrook Frequency
2 days	0	1
5 days	2	1
6 days	5	0
7 days	9	1
8 days	17	2
9 days	23	1
10 days	15	1
11 days	8	2
12 days	8	1
13 days	5	2
14 days	5	0
15 days	6	1
16 days	4	0
17 days	3	0
18 days	4	0
19 days	1	0
20 days	2	0
22 days	1	0
23 days	1	0
24 days	1	0
25 days	1	0
26 days	3	0
27 days	2	0
28 days	2	0
29 days	3	0
30 days	2	0
31 days	1	0
33 days	1	0
43 days	1	0
57 days	1	0

The @RISK software tool was used to derive the duration of illness submodel for Q fever from the data provided in Table 31. The best fit to the data was determined to be a lognormal probability distribution with a mean incubation period of 12.1 days and standard deviation of 6.66 days. The CDF of this lognormal distribution is:

$$F(t) = \frac{1}{2} + \frac{1}{2}\text{erf}\left[\frac{\ln(t) - \mu}{\sigma\sqrt{2}}\right]$$

where:

F is the cumulative fraction of ill persons who have completed the course of disease,

t is the duration [days],

μ is the mean of the variable's natural logarithm [= 2.36],

σ is the standard deviation of the variable's natural logarithm [= 0.516], and

erf is the error function where $\text{erf}(x) = \frac{2}{\sqrt{\pi}} \int_0^x e^{-t^2}\, dt$.

Figure 11 illustrates the distribution and fit to the original data.

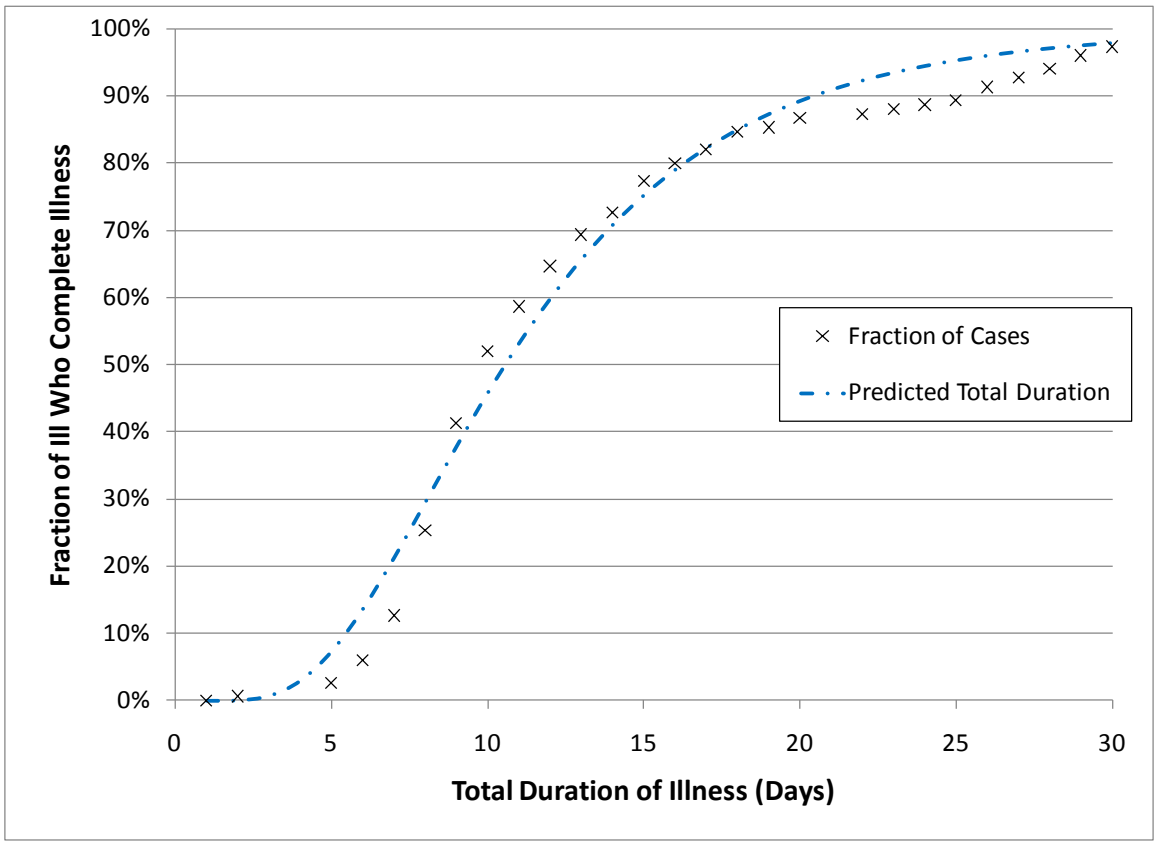

Figure 11. Q Fever Duration

H. Medical Countermeasures and Treatment

Both antibiotic prophylaxis and vaccination appear effective in preventing Q fever. The *AMedP-8 (Biological) Methods Report* states that both vaccination and antibiotic

prophylaxis are appropriate prophyalxis measures.[175] *Medical Aspects of Biological Warfare* states that the Q-vax® vaccine, licensed for use in Australia, is completely effective.[176] Since both vaccine therapy and antibiotic prophylaxis appear to be 100% effective, prophylaxis was modeled as 100% effective.

I. Summary and Conclusions

The parameters described in this chapter were derived from a collection of articles which include analyses of controlled human exposures to Q fever, as well as analyses of cases, outbreaks, and the microbiological characteristics of Q fever. The controlled human exposure data, however, was never completely published, and leads to some inconsistencies between this study and previous analyses. It is the recommendation of the authors to use the parameters described here, but that the complete controlled human exposure data be collated and published to allow for a thorough analysis to derive the human response parameters of interest. Once that is complete, it may be of value to then pursue a research program to further quantitatively characterize the infectivity, lethality, incubation, duration, and course of illness of Q fever.

Based on the available data, analysis and literature review as described in the preceding sections, the authors recommend using the parameter values provided in Table 32 to model Q fever in humans. The illness profile for Q fever, provided in Section F, is repeated in Table 33.

Table 32. Q Fever Model Parameters Summary Table

Submodel	Type	Parameters
Infectivity	Lognormal distribution	ID_{50} = 30 organisms; Probit slope = 30.782 probits/log(dose)
Lethality	Rate	0%
Incubation period	Log-linear function	$\alpha = 19.6$, $\beta = -1.88$
Duration of illness	Lognormal distribution	$\mu = 2.4$, $\sigma = 0.51$

[175] Anno et al., *AMedP-8 (Biological) Methods Report*, 21.

[176] Waag, "Q Fever," in *Medical Aspects of Biological Warfare*, 206.

Table 33. Q Fever Illness Profile

	Stage 1
Signs and Symptoms (S/S)	Fever, chills, headache, myalgia Pneumonia; hepatitis
S/S Severity	2 (Moderate)
Outlook	Patient is likely to recover

5. Staphylococcus Enterotoxin B (SEB)

This chapter presents the proposed human response model parameter values for Staphylococcal enterotoxin B (SEB), the fourth of five agents discussed in this document. It describes the results of the literature review and data analyses conducted by the IDA study team in the acquisition and derivation of these values.

A. Background

Staphylococcal enterotoxin B (SEB) is secreted by the gram-positive bacteria *Streptococcus pyogenes* and *Staphylococcus aureus*. SEB is one of the class of bacterial products called "superantigens" because of their profound effects upon the immune system. Most strains of *S. aureus* and *S. pyogenes* examined harbor genes for superantigens and are likely to produce at least one of these products. The staphylococcal enterotoxins are most frequently associated with food poisoning, yet not all superantigens are enterotoxins, and more severe physiological consequences, such as a life-threatening toxic shock syndrome (TSS), may result from exposure to any of the superantigens through a nonenteric route.[177] The pulmonary form of SEB intoxication that results from inhaling the aerosol form results in a markedly different clinical syndrome than if the toxin is ingested. SEB, not generally thought of as a lethal agent, is classified as an incapacitant. However, inhalational SEB intoxication can seriously debilitate humans causing various degrees of performance decrement for a week or more depending on the inhaled dose and individual variability.[178] High dose, microgram-level exposures to SEB will result in fatalities, and inhalation exposure to nanogram or lower levels may be severely incapacitating.[179]

B. Primary References and Data Sets

Three of the four "capstone" documents listed in Table 3 informed the development of the human response model for inhalational SEB intoxication: *Medical Aspects of*

[177] Robert G. Ulrich et al., "Staphylococcal Enterotoxin B and Related Toxins," in *Medical Aspects of Biological Warfare*, 311–322.

[178] Anno et al., *AMedP-8 (Biological) Methods Report*," 13.

[179] Ulrich et al., "Staphylococcal Enterotoxin B and Related Toxins," in *Medical Aspects of Biological Warfare*, 312.

Biological Warfare,[180] the *AMedP-8 (Biological) Methods Report*, and *Consequence Analytic Tools for NBC Operations*.[181]

In addition, the authors relied heavily on infectivity and lethality studies published in a previously classified reference and clinical descriptions of the symptoms of nine victims of accidental exposure to aerosolized SEB, described in:

- "Joint CB Technical Data Source Book, Volume VI, Toxin Agents, Part Two: Agent PG (U)" (Desert Test Center, Fort Douglas, Utah, February 1973).
- Sidell, S., "Human Clinical Syndrome Associated with Accidental Exposure to Aerosolized Staphylococcal Enterotoxin B," in Dangerfield, H. G. (Ed.) *Special Report to Commission on Epidemiological Survey*, No. 65-FDS-1662 (Ft. Detrick, Frederick, MD, April 1965).

Combined, this included human dose response data from animal exposure studies, military research volunteers (MRV), and accidental exposures.

The *AMedP-8 (Biological) Methods Report* includes a summary table of the MRV dose data for the 59 MRV participants, but does not provide any specific data on effectivity or lethality of SEB as a function of dose.[182] The focus of the *AMedP-8 (Biological) Methods Report* was on the MRV case data to support development of models quantifying human response to inhaled SEB. Clinical records and charts of 63 MRV cases were obtained from the United States Army Medical Research Institute for Infectious Disease (USAMRIID) by researchers at Pacific Sierra Research Corporation. A request has been submitted to review the actual clinical records for this, but IDA researchers have not yet been granted access to the raw data.

Clinical descriptions of the symptoms of nine accidental exposure victims, referenced in both *Medical Aspects of Biological Warfare*[183] and the *AMedP-8 (Biological) Methods Report*,[184] were available in the Sidell report, and proved fundamental to the analyses, recommendations, and conclusions presented here. Rusnak et al.[185] discusses clinical records for additional accidental exposure cases (up to seven more inhalational cases), but those cases were not described at the level of clinical detail

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[180] Ibid., 311–322.

[181] The two PSR references provide identical information related to SEB; any references to this information in the sections that follow cite the more recent *AMedP-8 (Biological) Methods Report*.

[182] Anno et al., *AMedP-8 (Biological) Methods Report*, 115.

[183] Ulrich et al., "Staphylococcal Enterotoxin B and Related Toxins," in *Medical Aspects of Biological Warfare*, 317.

[184] Anno et al., *AMedP-8 (Biological) Methods Report*, 13–14.

[185] J. M. Rusnak et al., "Laboratory Exposures to Staphylococcal Enterotoxin B," *Emerging Infectious Diseases* 10 (2004): 1544–49.

available in Sidell and required for the development of the SEB submodels. A request to review these case files was included as part of the request for the MRV clinical records – IDA is still waiting for permission to review that data.

It is clear that more data exists than was reviewed by the authors of this study, and this data should be reviewed to validate or update the models and parameters proposed in this study for modeling and simulation of human response and casualty estimation planning. In particular, there is very little human dose-response data across the full range of doses from ineffective to supra-lethal. This lack of data leads to potentially weak models for effectivity, lethality, latent period, and disease duration, where the models may not properly account for dose dependence. Alternatively, there seems to be very good (if limited) data for the signs and symptoms resulting from inhalation of SEB, which enhances the authors' confidence in the proposed illness profile submodel.

C. Effectivity

As described in the *AMedP-8 (Biological) Methods Report*, experiments with MRVs have shown that for aerosol SEB exposure the median effective dose, or ED_{50} (dose capable of incapacitating 50% of the exposed human population), is 0.026 μg/70 kg man (about 0.0004μg/kg).[186] The *AMedP-8 (Biological) Methods Report* proposed that this dose response be represented with a lognormal distribution with this median effective dose and a probit slope (probits/logarithm of dose) equal to 2.44 (μ = -3.64, σ = 0.942).[187]

The *Sourcebook* provides raw data for respiratory exposure of humans to SEB (see Table 34) though the description of the experiment is not provided. The total dose received is based upon an agent purity of 95 to 99 %.

Table 34. Human Respiratory Exposure Data for SEB

Total Dose Received (μg)	Number of Individuals Ill over Total Exposed
0.001	0/4
0.003	0/2
0.01	0/2
0.02	4/8
0.03	4/8
0.05	6/8

[186] Anno et al., *AMedP-8 (Biological) Methods Report*, 94.

[187] Ibid.

Based upon these human respiratory data, the *Sourcebook* authors calculate the probit slope to be 2.54 and the Median Man Respiratory Infective Dose ($MRID_{50}$) to be 0.026 μg,[188] which corresponds to the ED_{50} found in open literature. The 95% confidence interval for the $MRID_{50}$ is [0.017–0.041].

Using these data with the methodology outlined in Tallarida,[189] IDA calculates a probit slope of 2.54 and ED_{50} of 0.026 μg, which match the values found in the *Sourcebook*. This study recommends, both for the purpose of defining a precise modeling parameter and for estimating casualties within the *AMedP-8(C)* methodology, the effectivity of inhaled SEB be characterized by a lognormal distribution with an ED_{50} of 0.026 μg and a probit slope equal to 2.54 probits per logarithm of dose.

The corresponding CDF of the lognormal distribution used to model the aerosol infectivity of SEB in humans is:

$$F(d) = \frac{1}{2} + \frac{1}{2}\text{erf}\left[\frac{\ln(d) - \mu}{\sigma\sqrt{2}}\right]$$

where:

F is the cumulative fraction of persons who have become infected with SEB,

d is the effective dose [μg],

μ is the mean of the variable's natural logarithm [= $\ln(ED_{50})$ = ln(0.026 μg) =-3.65],

m is the probit slope [= 2.54 probits/log(dose)],

σ is the standard deviation of the variable's natural logarithm [= $e^{1/m}$ = $e^{1/2.54}$ = 1.48], and

erf is the error function where $\text{erf}(x) = \frac{2}{\sqrt{\pi}}\int_0^x e^{-t^2}\,dt$.

D. Lethality

No lethality studies have been conducted on humans, but the *Sourcebook* cites several experiments on rhesus monkeys that catalogue illness endpoints based on SEB dose. The assumed relationship between human and primate response and the measured data from these studies were then used to extrapolate human response estimates.

[188] "Joint CB Technical Data Source Book, Volume VI, Toxin Agents, Part Two: Agent PG (U)" (Deseret Test Center, Fort Douglas, Utah, February 1973).

[189] Tallarida.

In a series of experiments collected to evaluate the storage life of SEB the following tables are given:[190]

Table 35. Rhesus Monkey Responses to 95% Pure SEB Intravenously Injected

Response		10 Tests	12 Tests
Emesis	ED_{50} (μg/kg)	0.28 (0.13–0.62	0.27 (0.13–0.59)
	Probit slope	0.55 (0.4–0.7)	0.52 (0.38–0.66)
Diarrhea	ED_{50} (μg/kg)	28.08 (5.6–142)	56.4 (9.8–323)
	Probit slope	0.3 (0.15–0.44)	0.29 (0.16–0.43)
Depression	ED_{50} (μg/kg)	142.7 (32.2–632)	138.4 (37–517)
	Probit slope	0.49 (0.31–0.66)	0.51 (0.34–0.68)
Death	LD_{50} (μg/kg)	19.8 (15.2–25.7)	24.4 (19–31.3)
	Probit slope	1.91 (1.4–2.42)	1.92 (1.41–2.42)

Table 36. Mean Responses of Animals to 95% Pure SEB

	Route			
	Intavenous		Respiratory	
Species	ED_{50} (μg/kg)	LD_{50} (μg/kg)	ED_{50} (μg/kg)	LD_{50} (μg/kg)
Rhesus	0.26	24	6.1	27
Cynomologous	0.08	11.1	3.3	12
Beagle	0.05	1560	0.65	45
Swine	1.4	144	>20	>20
Chimpanzee	12–40	….	9–22	>81

The *Sourcebook* makes the assumption that human response is proportional to the responses observed in the non-human primate models (specifically, rhesus macaques). Using the methodology described in Chapter 3 of the *Sourcebook* and the data provided in Table 35 and Table 36 (substituting RIVID, rhesus intravenous effective/infective dose for RIVFID), the $MRLD_{50}$ estimate is 2.4 μg.

$$\frac{RIVID_{50}}{RIVLD_{50}} = \frac{MRID_{50}}{MRLD_{50}}$$

$$MRLD_{50} = MRID_{50} \times \frac{RIVLD_{50}}{RIVID_{50}} = 0.026 \times \frac{24}{0.26} = 2.4\mu g$$

[190] "Joint CB Technical Data Source Book," 4–3.

The *Sourcebook* explicitly estimates a Median Man Respiratory Lethal Dose ($MRLD_{50}$) of 39 μg by using rhesus monkey response from a 1966 study and assuming that the ratio between rhesus intravenous fever illness dose ($RIVFID_{50}$ = 0.05) and rhesus median intravenous lethal dose ($RIVLD_{50}$ = 75) is the same as the ratio between $MRID_{50}$ and $MRLD_{50}$.

$$\frac{RIVFID_{50}}{RIVLD_{50}} = \frac{MRID_{50}}{MRLD_{50}}$$

$$MRLD_{50} = MRID_{50} \times \frac{RIVLD_{50}}{RIVFID_{50}} = 0.026 \times \frac{75}{0.05} = 39\mu g$$

An additional $MRLD_{50}$ estimate of 1.66 μg was derived from rhesus monkey respiratory doses at Ft. Detrick, Maryland, and used in later handbooks. The dose values assumed in this calculation are provided in Table 37. [191]

Table 37. Dose Values of Illness Effects

	Description	Value (μg)
$RRFID_{50}$	Median Rhesus Respiratory Fever Illness Dose	1.17 (calculated)
$RREDID_{50}$	Median Rhesus Respiratory Emesis-Diarrhea Illness Dose	18.3
$RIVFID_{50}$	Median Rhesus Intravenous Fever Illness Dose	0.05
$RIVEID_{50}$	Median Rhesus Intravenous Emesis-Diarrhea Illness Dose	0.78
$RRLD_{50}$	Median Rhesus Respiratory Lethal Dose	75
$MRID_{50}$	Median Man Respiratory Infective Dose	0.026

$$\frac{RRFID_{50}}{RREDID_{50}} = \frac{RIVFID_{50}}{RIVEDID_{50}}$$

$$RRFID_{50} = RREDID_{50} \times \frac{RIVFID_{50}}{RIVEDID_{50}} = 18.3 \times \frac{0.05}{0.78} = 1.17\mu g$$

$$\frac{RRFID_{50}}{RRLD_{50}} = \frac{MRID_{50}}{MRLD_{50}}$$

$$MRLD_{50} = MRID_{50} \times \frac{RRLD_{50}}{RRFID_{50}} = 0.026 \times \frac{75}{1.17} = 1.66\mu g$$

The probit slope for both of these lethal dose estimates is 3 probits per log dose.[192] Using these data, IDA recommends, both for the purpose of defining a precise modeling

[191] Ibid., 3–5.

[192] Ibid.

parameter and for estimating casualties within the *AMedP-8(C)* methodology, the lethality of inhaled SEB be characterized by a lognormal distribution with an LD_{50} of 1.66 μg and a probit slope equal to 3.00 probits per logarithm of dose. (On a side note, for a 70 kg man 1.66 μg is equivalent to 0.02371 μg/kg. Rusnak, a more recent reference, uses this value of 0.02 μg/kg to estimate the LD_{50} as 1.4 μg/70 kg man.[193])

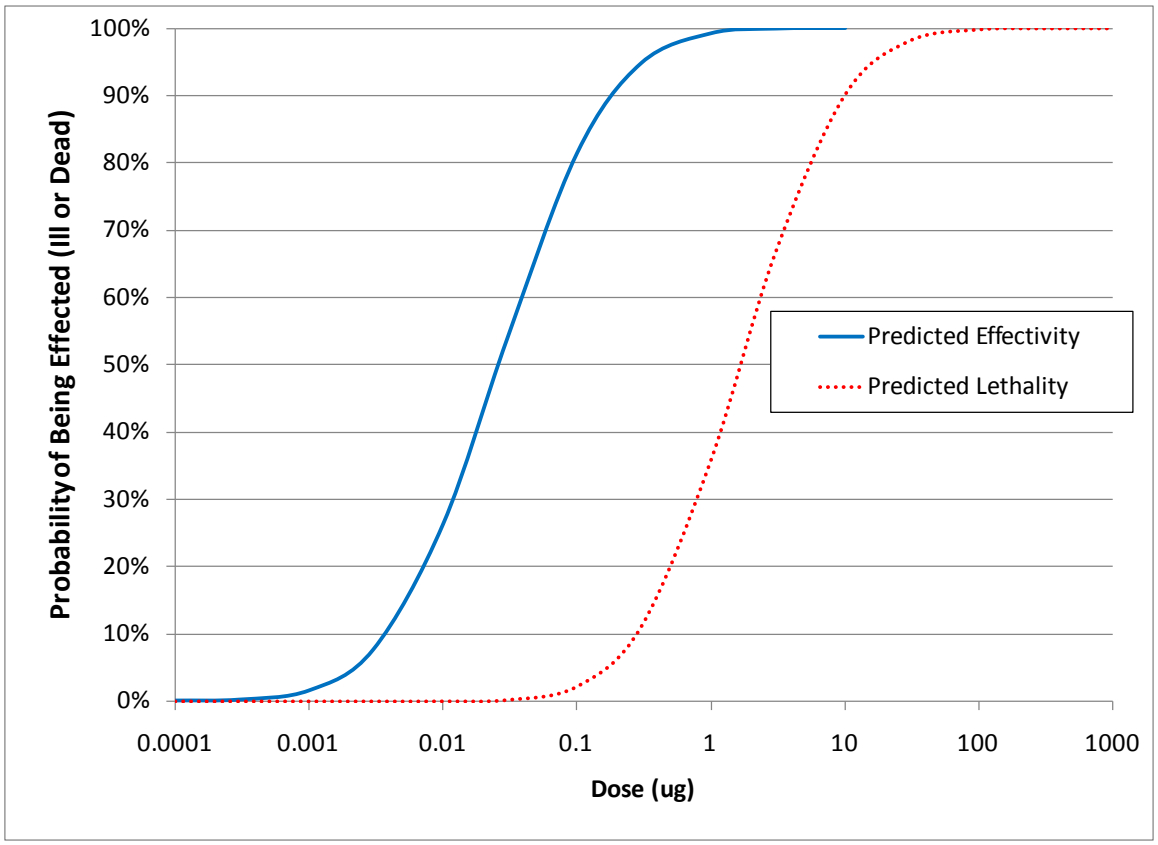

Figure 12. SEB Effectivity and Lethality

E. Latent Period

Although there is no definitive data available in the open literature from which to validate the dose response distributions for effectivity and lethality, there is data available which describes laboratory accidents and the resulting signs and symptoms resulting from these aerosol exposures.[194] Nine individuals were exposed to SEB in a 1964 laboratory accident, and their recorded sign and symptoms were used to describe the progress of the

[193] Rusnak et al., "Laboratory Exposures to Staphylococcal Enterotoxin B," 1548.

[194] S. Sidell, "Human Clinical Syndrome Associated with Accidental Exposure to Aerosolized Staphylococcal Enterotoxin B," in Dangerfield, H. G. (Ed.) *Special Report to Commission on Epidemiological Survey*, No. 65-FDS-1662 (Ft. Detrick, Frederick, MD, April 1965): 13.

disease, once intoxication has occurred. (The specific clinical descriptions for the nine cases from Sidell are provided in Appendix A.)

The *AMedP-8 (Biological) Methods Report* describes inhalational SEB intoxication as occurring "quickly compared to other biological agents, within 3 to 11 hours post exposure."[195] *Medical Aspects of Biological Warfare* describes the disease as "A severely incapacitating illness of rapid onset (3–4 hours) and modest acute duration (3–4 days)."[196] From the nine accidental exposure cases described by Sidell, it is possible to estimate the time of onset of the various symptoms, as shown in Table 38. The same estimates are made by Ulrich et al., and are also shown, for comparison.

Table 38. SEB Symptom Onset Times (hours post exposure)

	Sidell				Textbook of Military Medicine			
Symptom	**Avg**	**SD**	**Min**	**Max**	**Avg**	**SD**	**Min**	**Max**
Cough	9.09	5.75	1	19.75	10.4	5.4	NR	NR
Elevated Temperature	12.97	2.81	10.5	19.75	12.4	3.9	8.0	20.0
Chills	9.44	2.26	7	12	Not Reported			
Headache	9.47	4.64	5	19.75	13.3	10.0	4.0	36.0
Nausea	13.38	6.81	7	23.75	17.0	6.3	8.0	24.0
Myalgia	10.75	3.50	7	15	13.0	5.0	8.0	20.0
Malaise	11.59	4.34	7	19.75	Not Reported			
Chest Pain	9.00	1.90	7	12	12.0	6.5	NR	NR
Vomiting	13.17	6.01	7	19	14.0	5.1	8.0	20.0
Anorexia	14.88	6.73	7	23.75	18.5	5.6	8.0	24.0
Dyspnea	19.50	24.39	7	63	Not Reported			

Note that the Sidell report provides data on both a symptom described as "Feverish," as well as the measured temperatures for each case, while *Medical Aspects of Biological Warfare* includes a "fever" symptom. The values in Table 38 are for the time of elevated temperatures from Sidell (which was first measured at the time of hospital admission), and fever from *Medical Aspects of Biological Warfare*. For the six of nine cases described by Sidell which were "Feverish," the average time of onset for "Feverish" was 12.6 hours post exposure (standard deviation = 3.83, minimum = 9, maximum = 19.75 hours).

[195] Anno et al., *AMedP-8 (Biological) Methods Report*.

[196] Ulrich et al., "Staphylococcal Enterotoxin B and Related Toxins," in *Medical Aspects of Biological Warfare*, 317.

The latent period is defined as the time from exposure to the onset of illness. From IDA's analysis of the accidental exposure cases reported by Sidell, the time of exposure is uncertain: exposure occurred during one or both of the periods of animal exposure (0900–1030 hours and 1300–1430 hours). For the purposes of this analysis, the time of exposure for all cases was assumed to be 0900 hours.

From the signs and symptoms described by Sidell, several estimates of the latent period could be made, depending on the definition used for what constitutes the onset of illness. From the data presented, there seem to be at least five different times which can be defined as the "start" of illness (and thus the end of the latent period):

- The time reported for the start of the earliest symptom. Using this as the onset of illness, the average latent period across all cases is 7.33 hours (SD = 3.64; Minimum = 1; Maximum = 12 hours).
- The time reported for the start of the last symptom, indicating that all symptoms are present. Using this as the onset of illness, the average latent period across all cases is 20.69 hours (SD = 16.35; Minimum = 10.5; Maximum = 23.75 hours).
- The average time reported for the start of all of the signs and symptoms experienced. Using this as the onset of illness, the average latent period across all cases is 11.76 hours (SD = 4.58; Minimum = 7.05; Maximum = 19.36 hours).
- The time reported for the "Clinical Onset" for each case. Using this as the onset of illness, the average latent period across all cases is 9.50 hours (SD = 2.74; Minimum = 7; Maximum = 13.5 hours).
- The time reported for the "Hospital Admission" for each case. Using this as the onset of illness, the average latent period across all cases is 12.36 hours (SD = 3.09; Minimum = 9; Maximum = 19.75 hours).

Table 39. SEB Latent Period Estimates (hours post exposure)

Case #	Earliest Sign or Symptom	Hours Post Exposure	Latest Sign or Symptom	Hours Post Exposure	All Symptoms Avg Hours Post Exposure	"Clinical Onset"	Hospital Admission
1	Cough	4	Elevated Temp	10.5	7.05	7	10.5
2	Headache	5	Dyspnea, Elevated Temp	11.5	9.75	10	11.5
3	Cough	1	Myalgia	15	7.61	7	10.5
4	Chest Pain, Cough	7	Anorexia	15	9.78	7	11.5
5	Chills, Anorexia, Headache, Cough	7	Elevated Temp	13.5	8.30	7	13.5
6	Feverish, Chills, Headache, Chest Pain, Cough	9	Malaise	15	11.00	9	9
7	Chest Pain	9	Anorexia, Nausea	23.75	19.36	13	19.75
8	Chills, Feverish, Malaise, Headache, Chest Pain, Cough	12	Dyspnea	63	18.10	12	12
9	Chills, Myalgia, Cough	12	Anorexia, Nausea, Vomiting	19	14.88	13.5	13
Average		7.33		20.69	11.76	9.50	12.36
Std. Dev.		3.64		16.35	4.58	2.74	3.09

The *AMedP-8 (Biological) Methods Report* regards body temperature as a reliable quantitative indicator of SEB intoxication. With this assumption, "Onset was assumed to occur at the time point just prior to a sequential series of at least three measurements of [body temperature greater than or equal to] 100°F."[198] The *AMedP-8 (Biological) Methods Report* models the latent period as a linear function of dose within the dose range of 0.01 to 0.15 μg.[199] The dose dependent time of onset (latent period) is expressed in the form of:

$$t_0 = \alpha + \beta \mathrm{D}$$

where:

t_o = time to onset of illness (hours);

D = dose (μg)

α = 9.2837; and

β = -58.0883.

At doses below this range, the *AMedP-8 (Biological) Methods Report* recommends that 9 hours is a reasonable estimate for the latent period. At doses above this range, The *AMedP-8 (Biological) Methods Report* recommends that 30 minutes is a reasonable estimate for the latent period.

IDA's analysis of nine cases of accidental exposure does not appear to agree with the *AMedP-8 (Biological) Methods Report* model. Using their own febrile illness model, the *AMedP-8 (Biological) Methods Report* estimates the dose to 13 accidental exposure cases (which presumably included the nine reported by Sidell) as between 0.048 to 0.371 μg, based upon the maximum body temperature and febrile duration. Eight of the 13 are estimated to have received more than 0.15 μg, and therefore would have a time of onset of 30 minutes (or less). In the Sidell data, the minimum average time of symptom onset was 9 hours (for chest pain and cough). Even if the end of the periods of animal exposure (1430 hours) were used as the time of exposure, this would uniformly shift the time of onset by 5.5 hours, which would still not agree with the *AMedP-8 (Biological) Methods Report* model.

The recommendation of this study is to use the average time of "Clinical Onset" as identified by Sidell for the SEB latent period: it is felt that this best represents the medical opinion of those closest to the actual cases. For the purpose of defining a precise modeling parameter, this would define the latent period as equal to nine hours. For the purpose of estimating casualties within the *AMedP-8(C)* methodology, the latent period

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[198] Anno et al., *AMedP-8 (Biological) Methods Report*, 63.

[199] Ibid., 101.

can be characterized as equal to nine hours, or could be regarded as occurring on the first day.

F. Illness Profile

These nine accidental exposure cases exhibited, to varying degrees: fever, chills, malaise, myalgia, anorexia, nausea, vomiting, headache, chest pain, cough (productive and / or nonproductive), and dyspnea. Rusnak, et al. considered these nine cases, as well as seven others, and reported on the frequency with which these symptoms occurred in the sixteen cases, shown in Table 40. [200]

Table 40. Incidence of Signs and Symptoms Among Laboratory Accidental Exposures

Signs and Symptoms	Total (%)[†]
Cough	15/16 (93.7)
Fever	15/16 (93.7)
Chills	13/16 (81.3)
Headache	13/16 (81.3)
Nausea	12/16 (75.0)
Myalgia	11/16 (68.7)
Malaise	9/14 (64.3)
Chest pain	8/14 (57.1)
Vomiting	9/16 (56.3)
Anorexia	9/16 (56.3)
Dyspnea	8/16 (50.0)

[†]Some of the cases had no data reported for some symptoms, thus the denominator may be less than 16.

From this, it is clear that the common signs and symptoms of inhalational SEB intoxication include cough, fever, chills, headache, nausea, myalgia, malaise, chest pain, vomiting, anorexia and dyspnea. (Note that *Medical Aspects of Biological Warfare* does not include chills, malaise, or dyspnea on the list of common SEB signs and symptoms.[201]) Many other symptoms, such as fatigue, wheezing, abdominal cramps, diarrhea, gas, hepatitis, pharyngeal injection, rhinorrhea, postnasal drip, or sinus congestion, sore throat, otitis, hoarseness, conjunctival injection, burning eyes, and flushed face, may also occur. All of these occur rapidly, in the first few hours post exposure.[202]

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[200] Rusnak et al., "Laboratory Exposures to Staphylococcal Enterotoxin B," 1546.

[201] Ulrich et al., "Staphylococcal Enterotoxin B and Related Toxins," in *Medical Aspects of Biological Warfare*, 317.

[202] Ibid., 317.

Within the *AMedP-8(C)* methodology, the illness profile characterizes the disease by the stages manifest in the progress of the disease, the signs and symptoms exhibited within each disease stage, and the severity of the overall presentation for each stage. This study recommends defining Stage 1 of inhalational SEB intoxication as including nausea, vomiting, chills, dyspnea, chest pain, myalgia, headache, anorexia, malaise, elevated temperature and cough. Because the accidental exposure cases received hospital care until these symptoms were resolved (except cough), this stage should be characterized as Severity Level 3.

This study recommends defining Stage 2 of inhalational SEB intoxication as including only cough, and only for the survivor cohort. Based upon the accidental exposure cases being released from the hospital and provided minimal care at home, this stage should be characterized as Severity Level 1.

For non-survivors, there would be no recovery from Stage 1 of inhalational SEB intoxication; Stage 2 would be death.

Table 41. Illness Profile for Inhalational SEB Intoxication

	Stage 1	Stage 2 (survivors)	Stage 2 (non-survivors)
Signs and Symptoms (S/S)	Cough, headache, chest pain, myalgia, elevated temperature, vomiting, nausea, and anorexia	Non-productive cough	None (Dead)
S/S Severity	Severity Level 3 (“Severe”)	Severity Level 1 (“Mild”)	
Outlook	Individual will progress to Stage 2	Individual will likely recover	Death

G. Illness Duration

The same data set from the nine accidental exposure cases can be used to estimate the duration of the signs and symptoms of SEB intoxication. Just as for the estimation of the latent period, it is possible to compare the values from the nine accidental exposure cases and the values reported by Ulrich et al. as shown in Table 42.[203]

[203] Ibid., 317.

Table 42. SEB Symptom Duration (hours)

	Sidell				Medical Aspects of Biological Warfare			
Symptom	**Avg**	**SD**	**Min**	**Max**	**Avg**	**SD**	**Min**	**Max**
Cough	223.84	140.38	51	515	92.0	41.0	NR	NR
Elevated Temperature	69.86	25.80	39	124.5	50.0	22.3	12.0	76.0
Chills	12.37	9.22	5	32	Not Reported			
Headache	40.03	16.77	10	56	30.6	19.0	8.0	60.0
Nausea	12.71	10.05	5	32	9.0	5.5	4.0	20.0
Myalgia	39.12	13.34	27	56	16.0	15.0	4.0	44.0
Malaise	66.41	32.73	29	123	Not Reported			
Chest Pain	34.00	45.26	5	123	23.0	27.0	4.0	84.0
Vomiting	9.33	2.31	8	12	Reported as None (Single Event)			
Anorexia	52.12	40.34	8	117.5	44.5	45.0	4.0	136.0
Dyspnea	25.50	20.25	3	56	Not Reported			

As before, the values in Table 42 are for the duration of elevated temperatures from Sidell, and fever from *Medical Aspects of Biological Warfare*. For the six of nine cases described by Sidell which were "Feverish," the average duration for "Feverish" was 10.79 hours (standard deviation = 7.66, minimum = 1.5, maximum = 19.25 hours). Note also that Ulrich states that vomiting was observed as a single emetic event, and therefore would have no duration.

The duration for which SEB is a manifest illness must be defined as a function of these signs and symptoms, but it is open to interpretation as to which specific signs or symptoms would be used. A review of the average duration of each symptom would seem to group the symptoms into separate sets: nausea, vomiting, and chills endure 5 to 32 hours, with an average duration of about 9–12 hours. Dyspnea, chest pain, myalgia, headache, anorexia, malaise, and elevated temperature endure 3 to 125 hours, with an average duration of about one to three days. It appears reasonable to group all of these symptoms together as "Stage 1" of the disease, since some subset of the group of them together is what resulted in the cases being admitted to the hospital, and the release from the hospital was only made after all of these symptoms had cleared. Cough is the only symptom with an average duration (9.3 days) well in excess of three days, plus cough is the only symptom with which patients were discharged from the hospital.

With the assumption that body temperature indicates SEB intoxication, the *AMedP-8 (Biological) Methods Report* regards the illness as extending from the time of onset to

"when three successive temperature measurements occurred below 100°F."[204] The *AMedP-8 (Biological) Methods Report* models the illness duration as a linear function of dose within the dose range of up to 0.15 μg.[205] The dose-dependent duration of the febrile period is expressed in the form of:

$$\Delta t_f = \alpha + \beta D$$

where:

Δt_f = duration of the febrile period (hours);

D = dose (μg);

α = 6.0966; and

β = 371.4122.

At doses above this range, the *AMedP-8 (Biological) Methods Report* recommends that 60 hours is a reasonable estimate for the maximum duration of the illness.

From the signs and symptoms described by Sidell, several estimates of duration of the first stage of Inhalational SEB intoxication could be made, depending on the time used as the reference for the start sign or symptom. The different options available for defining the reference time for the start of signs and symptoms, in order to estimate the duration of Stage 1 of SEB intoxication, are:

- The time reported for the start of each individual symptom (less cough, as noted above).
  - From this, the duration of Stage 1 can be defined as the time from the start to end of each individual sign or symptom, and the average of all of these across all cases is 39.16 hours (SD = 14.72; Minimum = 17.29; Maximum = 59.28 hours).
  - A variation of this is to define, for each case, the reference start time as the average time all of the signs and symptoms considered start. From this, the duration of Stage 1 is defined as the difference between the average start time to the average end time, and the average of all of these across all cases is 38.84 hours (SD = 14.30; Minimum = 17.29; Maximum = 59.28 hours).
  - Alternatively, the signs and symptoms which describe Stage 1 of Inhalational SEB intoxication could be regarded collectively (as a syndrome). For each case, the start time of Stage 1 would therefore be the time the first symptom of the syndrome appeared to the time the last

[204] Anno et al., *AMedP-8 (Biological) Methods Report*, 64.

[205] Ibid., 101.

symptom of the syndrome was resolved. The average of these across all cases is 89.17 hours (SD = 24.47; Minimum = 54; Maximum = 128 hours).

- The time reported for the “Clinical Onset” for each case.
  - From this, the duration of Stage 1 can be defined for each case as the average of the differences from “Clinical Onset” to end of each considered sign or symptom, and the average of all of these across all cases is 42.03 hours (SD = 14.87; Minimum = 17; Maximum = 66.06 hours).
  - Alternatively, the duration of Stage 1 can be defined for each case as the average of the differences from “Clinical Onset” to end of all considered signs or symptoms (collectively), and the average of all of these across all cases is 88.61 hours (SD = 25.01; Minimum = 54; Maximum = 128 hours).
  - A third variation on this is to consider Stage 1 of Inhalational SEB intoxication as complete upon the end of hospitalization. For this, the duration of Stage 1 is defined for each case as the duration from the time of “Clinical Onset” to the time of hospital discharge, and the average of all of these across all cases is 138.11 hours (SD = 29.87; Minimum = 90; Maximum = 188 hours).
- The time reported for the “Hospital Admission” for each case. The logical duration for this start time is the time of hospitalization, which for each case would be from the time admitted to the time discharged. The average of all of these across all cases is 134.03 hours (SD = 31.40; Minimum = 79.25; Maximum = 184.50 hours).

Table 43. Estimates of Different Definitions of Stage 1 of Inhalational SEB Intoxication Duration

Start Time	End Time	Duration (hours) (For All Cases)			
(By Each Case)		Avg	Std Dev	Min	Max
Start of Each Sign or Symptom, Individually	End of Each Sign or Symptom, Individually	39.16	14.72	17.29	59.28
Average Start of the Signs and Symptoms	Average End of the Signs and Symptoms	38.84	14.30	17.29	59.28
Start of the Syndrome of Signs and Symptoms, Collectively (= Start of First Sign or Symptom)	End of the Syndrome of Signs and Symptoms, Collectively (= End of Last Sign or Symptom)	89.17	24.47	54.00	128.00
"Clinical Onset"	End of Each Considered Sign or Symptom	42.03	14.87	17.00	66.06
"Clinical Onset"	End of All Considered Signs or Symptoms	88.61	25.01	54.00	128.00
"Clinical Onset"	Hospital Discharge	138.11	29.87	90.00	188.00
Hospital Admission	Hospital Discharge	134.03	31.40	79.25	184.50

Note that if the *AMedP-8 (Biological) Methods Report* model is modified to extend up to a dose 0.50 μg, the febrile duration is approximately equal to 192 hours (8 days) (shown in Figure 13). This is in reasonable agreement with IDA's analysis of the nine cases of accidental exposure (particularly considering the *AMedP-8 (Biological) Methods Report* estimate of the accidental dose range of 0.048 to 0.371 μg). Any of these estimates are in general agreement with the *Medical Aspects of Biological Warfare* estimate of three to four days.

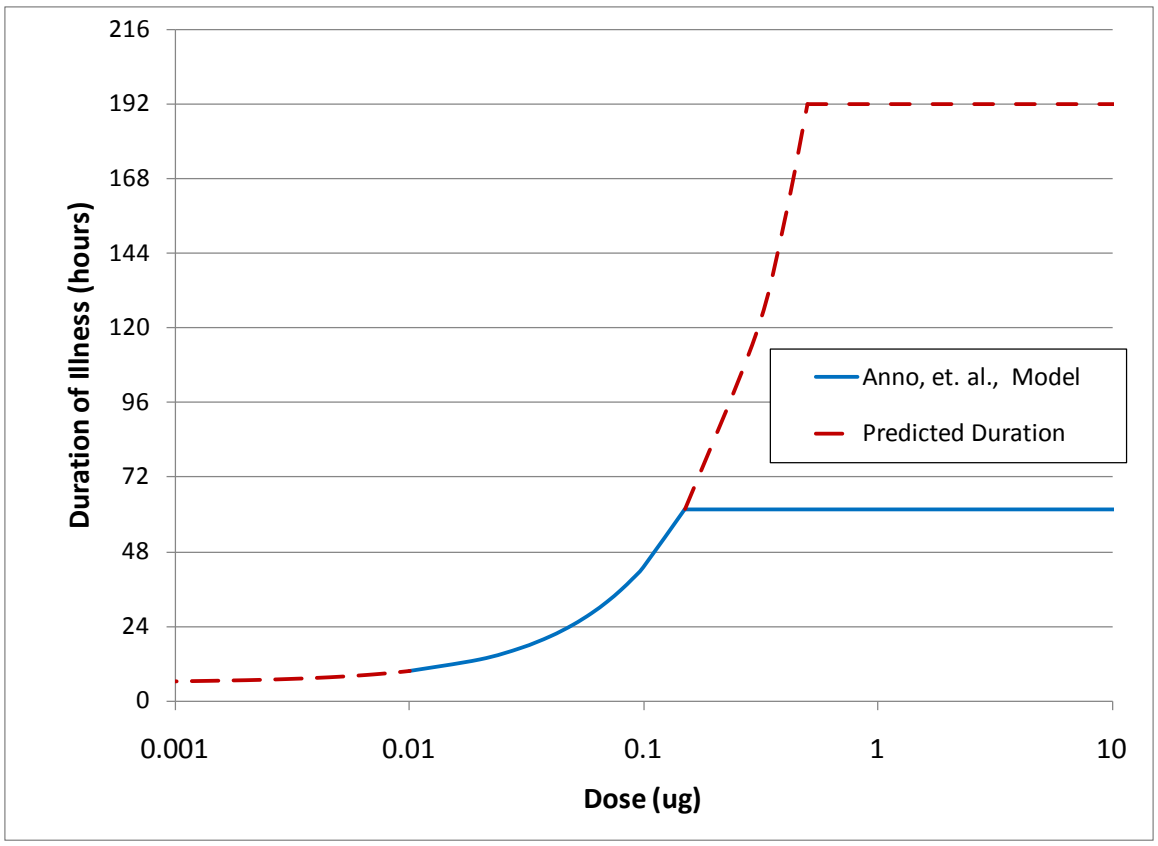

Figure 13. SEB Duration of Stage 1 of Illness

The recommendation of this study is to use this modification of the *AMedP-8 (Biological) Methods Report* model to represent the duration of Stage 1 of SEB intoxication. It is felt that this corresponds well with defining duration as extending from the time defined in the Sidell Report as "Clinical Onset," until the end of all considered signs or symptoms (except cough). For the purpose of defining a precise modeling parameter, and for estimating casualties within the *AMedP-8(C)* methodology, the duration of Stage 1 of inhalational SEB intoxication is:

$$\Delta t_{SEB\ Stg\ 1} = \alpha + \beta D$$

where:

$\Delta t_{SEB\ Stg\ 1}$ = Duration of Stage 1 of Inhalational SEB intoxication (hours);

D = dose (μg), for D <= 0.5 μg;

α = 6.0966; and

β = 371.4122

At doses above 0.5 μg, this study recommends that 192 hours (8 days) is a reasonable estimate for the maximum duration of the illness.

"Cough" is the only symptom with an average duration well in excess of 3 days (average = 223.84 hours (9.3 days), SD = 140.38; Minimum = 51; Maximum = 515 hours), plus cough is the only symptom with which patients were discharged from the hospital. It is apparent that for inhalational SEB intoxication, cough is the only symptom that should be considered as exhibited beyond the first stage of the disease. On average, the duration of cough (9.3 days) was more than a week longer than the average duration of all of the other symptoms (1.6 days). As a minimum estimate, the duration of cough as Stage 2 of inhalational SEB intoxication should be modeled as one week (7.0 days) beyond Stage 1.

H. Medical Countermeasures and Treatment

Treatments normally applied to toxic shock syndrome (TSS) caused by superantigens (including intravenous immune globulin) may be effective for treatment of inhalational SEB intoxication. Vaccines of SEB and Staphylococcal enterotoxin A (SEA) with altered critical residues involved in binding class II major histocompatibility complex molecules were also used successfully to vaccinate mice and monkeys against SEB-induced disease.[206] Otherwise, there appear to be little or no prophylactic or treatment regimens specifically targeted to this disease.

I. Summary and Conclusions

The parameters described in this chapter were derived from a very limited set of case reports from an accidental SEB exposure that occurred in 1964. There are published references to other data sets, including controlled animal and human exposures and additional accidental exposure cases. It is the recommendation of the authors to use the parameters described in this chapter, but that this additional data be collated and published (and declassified, if necessary) to allow for a thorough analysis to derive the human response parameters of interest. Once that is complete, it may be of value to then pursue a research program to further quantitatively characterize the infectivity, lethality, incubation, duration, and course of illness of SEB.

SEB is a biotoxin, and medical response is modeled more as a though it were a chemical agent than a replicating organism. The effectivity and lethality are modeled as lognormal functions of dose, while the latent period and duration of each stage of inhalational SEB intoxication are modeled as fixed values or linearly dependent upon dose. Recommended parameter values are summarized in Table 44. The illness profile for inhalational SEB intoxication, provided in Section F, is repeated in Table 45.

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[206] Ulrich et al., "Staphylococcal Enterotoxin B and Related Toxins," in *Medical Aspects of Biological Warfare*, 314.

Table 44. Inhalational SEB Intoxication Model Parameters Summary Table

Submodel	Type	Parameters
Infectivity	Lognormal distribution	ED_{50} = 0.026 μg; Probit slope = 2.44 probits/log(dose)
Lethality	Lognormal distribution	LD_{50} = 1.40 μg; Probit slope = 2.44 probits/log(dose)
Incubation period	Constant	9 hours
Duration of illness		
• Stage 1	Log-linear function	a = 6.10, b = 371 Maximum = 192 hours
• Stage 2	Constant	One week

Table 45. Illness Profile for Inhalational SEB Intoxication

	Stage 1	Stage 2 (survivors)	Stage 2 (non-survivors)
Signs and Symptoms (S/S)	Cough, headache, chest pain, myalgia, elevated temperature, vomiting, nausea, and anorexia	Non-productive cough	None (Dead)
S/S Severity	Severity Level 3 (“Severe”)	Severity Level 1 (“Mild”)	
Outlook	Individual will progress to Stage 2	Individual will likely recover	Death

6. Tularemia

This chapter presents the proposed human response model parameter values for tularemia, the last of five agents discussed in this document. It describes the results of the literature review and data analyses conducted by the IDA study team in the acquisition and derivation of these values.

A. Background

Tularemia is a zoonosis caused by the bacteria *Francisella tularensis*. Endemic to North America and Eurasia, tularemia was first investigated by researchers from the U.S. Public Health Service, including McCoy and Chapin, who in 1911 first isolated the bacteria from infected ground squirrels in Tulare County, California,[207] and Edward Francis, who pioneered research of the disease in humans.[208] The bacteria has four identified subspecies; Type A (*tularensis*) occurs predominantly in North America and is the most virulent subspecies in both animals and humans.[209] After tularemia was identified, diagnosis of the disease increased dramatically, with the incidence of reported cases of tularemia in the United States peaking at about 2,300 in 1939. Today, tularemia is rare in the United States, with only about 100 cases reported per year.[210]

Humans can acquire tularemia in a variety of ways: direct contact with infected animals or their tissues, ingestion of infected meat or contaminated water, animal bites or scratches, insect bites, and inhalation of contaminated aerosols.[211] Small mammals, such

[207] G. W. McCoy and C. W. Chapin, "Further Observations on a Plaguelike Disease of Rodents with a Preliminary Note on the Causative Agent *Bacterium tularense*," *Journal of Infectious Diseases* 10 (1912): 61–72.

[208] Edward Francis, "Tularemia," *The Journal of the American Medical Association* 84, no. 7 (1925): 1243–50. As Francis notes in his introduction, tularemia "is the only disease of man that has been elucidated from beginning to end by American investigators alone."

[209] Matthew J. Hepburn, Arthur M. Friedlander, and Zygmunt F. Dembek, "Tularemia," in *Medical Aspects of Biological Warfare*, 168.

[210] Richard Hornick, "Tularemia Revisited," *New England Journal of Medicine* 345, no. 22 (2001): 1638.

[211] Hepburn, Friedlander, and Dembek, "Tularemia," in *Medical Aspects of Biological Warfare*, 169.

as rabbits, hares, voles, mice, rats, and squirrels, are the natural reservoirs of infection, and they acquire tularemia via insect bites or contact with contaminated environments.[212]

Tularemia has a variety of clinical manifestations, depending to some extent on the route of infection (although symptoms overlap). The onset is typically abrupt, with a high fever, headache, chills and rigors, body aches, runny nose, and sore throat.[213] Francis described two types of infection:[214] glandular (or ulceroglandular), with enlarged glands and an evident local site of infection, and typhoidal, with symptoms similar to those associated with typhoid fever and without enlarged glands or observable local site of infection. This taxonomy was commonly used in published clinical studies of tularemia cases throughout the period of greatest incidence, but currently a more specific categorization is preferred.[215] Disease manifestations of tularemia are now generally divided into seven categories:[216]

- Ulceroglandular, characterized by a persistent ulcer at the site of infection combined with painful enlarged lymph nodes;
- Oculoglandular, similar to ulceroglandular but with the eye as the site of infection;
- Glandular, characterized by painful enlarged lymph nodes but without a cutaneous ulcer;
- Oropharyngeal, characterized by soreness and irritation of the throat and thought to be caused by ingestion of contaminated food or water;
- Pneumonic, characterized by pulmonary signs and symptoms consistent with pneumonia;
- Typhoidal, which presents as a nonspecific febrile syndrome; and
- Septic, which is the result of clinical progression of any other form of tularemia to a state of septic shock.

The pneumonic form of tularemia can occur directly from the inhalation of contaminated aerosols, or secondarily via the spread of the bacteria to the lungs from other parts of the body. Because exposure to biological warfare agents typically occurs via inhalation, the human response model of tularemia focuses on the pneumonic form.

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[212] David T. Dennis et al., "Tularemia as a Biological Weapon: Medical and Public Health Management," *Journal of the American Medical Association* 285, no. 21 (2001): 2764.

[213] Ibid., 2767.

[214] Francis, "Tularemia," 1246–47.

[215] Dennis et al., "Tularemia as a Biological Weapon: Medical and Public Health Management," 2767.

[216] Hepburn, Friedlander, and Dembek, "Tularemia," in *Medical Aspects of Biological Warfare*, 172–73.

This chapter describes information and models obtained from available literature that could be used to characterize each of these submodels in a human response model of primary pneumonic tularemia. From this information, parameter values are proposed to populate these submodels. In some cases, the proposed parameters may be considered placeholders pending the acquisition of additional data. In particular, IDA is currently in the process of gaining access to a set of controlled human experimental data from tularemia vaccine studies conducted with MRVs. Instances where proposed parameter values could be improved through the use of these data are noted in the following discussion.

B. Primary References and Data Sets

The authors relied extensively on all four of the "capstone" documents shown in Table 3 in the development of the tularemia human response model. The chapter on tularemia in *Medical Aspects of Biological Warfare*[217] and the *JAMA Consensus Statement on Tularemia*[218] are extensively referenced literature reviews conducted by groups of subject matter experts selected by the sponsoring organizations—the U.S. Army and the American Medical Association (AMA), respectively. These documents were used to identify authoritative sources of data for use in populating various submodels, including primary source data where possible.

In addition, IDA's research effort drew substantially on human response to tularemia work conducted by the Pacific Sierra Research Corporation (PSR) in support of earlier versions of AMedP-8 and documented in both the *AMedP-8 (Biological) Methods Report* and the earlier *Consequence Analytic Tools for NBC Operations*. The PSR analysis of tularemia data serves as the foundation for all subsequent work done by PSR in modeling human response to other biological agents, and it is perhaps the most extensively documented. Although the sources overlap greatly in their presentation of model parameters, *Consequence Analytic Tools for NBC Operations* contains some unique information and a fuller discussion of the underlying analysis; hence it is the document referenced in this study's discussion of tularemia submodel parameters.

PSR developed a stochastic, dose-dependent model of performance over time for individuals ill with tularemia; this model was derived from experimental data recorded during human testing of a tularemia vaccine with MRVs. Much of the MRV data remain unpublished, and as noted in Chapter 5, IDA researchers have not yet been granted to them.

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[217] Hepburn, Friedlander, and Dembek, "Tularemia," in *Medical Aspects of Biological Warfare*, 172–73.

[218] Dennis et al., "Tularemia as a Biological Weapon: Medical and Public Health Management," 2763–73.

The *AMedP-8(C)* biological human response models describe the progression of illness in the absence of treatment. Today, tularemia is readily cured by the administration of antibiotics, and modern clinical studies of the illness assume treatment. The authors therefore relied upon data published prior to the advent of routine antibiotic use for the characterization of mortality, illness profile, and duration of illness. While the incidence of tularemia in the United States peaked in this period and relevant data are prevalent, there are some difficulties associated with adapting this information for use in the model. Specifically, some of the most comprehensive clinical studies of tularemia were conducted when Francis' taxonomy of tularemia infections (glandular and typhoidal) was generally used, and before inhalation was understood to be a potential route of infection.

Patients with typhoidal tularemia were much more likely to develop pneumonia, at a rate of approximately 50%, versus those with ulceroglandular tularemia, only 12 to 15% of whom developed pneumonia.[219] The similarities in clinical manifestation of disease in typhoidal tularemia patients with pneumonia and in patients subjected to aerosol challenge vaccine studies suggested that at least some typhoidal tularemia patients had acquired disease via inhalation, although this point of view was somewhat controversial.[220]

While the route of exposure for typhoidal patients both with and without pneumonia remains a matter of speculation, the authors believe that historical data on typhoidal tularemia patients with pneumonia provide the best available data to characterize mortality, illness profile, and duration of illness within the tularemia human response model.

C. Infectivity

Both *Medical Aspects of Biological Warfare* and the *JAMA Consensus Statement on Tularemia* note that tularemia is remarkable for its low infectious dose, on the order of 10 organisms from either the cutaneous or the inhalation route of entry. Both cite the two published tularemia vaccine studies involving human volunteer subjects by Saslaw et al.,

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[219] Fred McCrumb, Jr., "Aerosol Infection of Man with *Pasteurella Tularensis*," *Bacteriological Review* 25 (1961): 262.

[220] Ibid. As McCrumb states: "It should be recognized that the mechanism of infection in so-called typhoidal tularemia is still a matter of controversy, there being those who doubt the importance or even the existence of primary pneumonic tularemia. One of the objectives of this presentation will be to marshal evidence in support of the concept that primary respiratory tularemia occurs as a naturally acquired as well as induced disease."

the first of which describes intracutaneous challenge[221] and the second of which describes respiratory challenge.[222]

In Saslaw's respiratory challenge study, 20 unvaccinated controls were exposed to 10 to 52 organisms via inhalation; of these, 16 became ill. The Saslaw data are provided in Table 46. Using these data and the maximum likelihood dose response calculation method described by Tallarida,[223] the authors derived an ID_{50}, of 6 organisms and probit slope (probits/logarithm of dose) equal to 1.47.

Table 46. Tularemia Respiratory Challenge Data[224]

Individual Dose (Organisms)	Response (Yes/No)
10	No
10	Yes
12	No
14	Yes
15	Yes
16	Yes
18	Yes
18	Yes
20	No
20	Yes
23	Yes
23	Yes
25	Yes
30	Yes
45	No
46	Yes
46	Yes
48	Yes
50	Yes
52	Yes

[221] Samuel Saslaw et al., "Tularemia Vaccine Study, I: Intracutaneous Challenge," *Archives of Internal Medicine 107* (1961): 121–33.

[222] Samuel Saslaw et al., "Tularemia Vaccine Study, II: Respiratory Challenge," *Archives of Internal Medicine 107* (1961): 134–46.

[223] Tallarida, "Quantal Dose-Response Data: Probit and Logit Analysis."

[224] Saslaw et al., "Tularemia Vaccine Study, II: Respiratory Challenge," 137, 140.

These results differ from those estimated in *Consequence Analytic Tools for NBC Operations*, which derived an ID_{50} of 10 organisms and probit slope of 1.93 for tularemia,[225] also using a maximum likelihood method of calculation but incorporating a broader set of unpublished human vaccine trial data, as noted above. These data include the Saslaw data set, as well 96 other cases with higher challenge doses, ranging from 315 to 62,000 organisms. All 96 of these cases had positive responses.

Perhaps because they had access to unpublished case histories, *Consequence Analytic Tools for NBC Operations* reports 22 cases from the Saslaw study, while the published data set includes only 20 cases. By comparing the table of low dose exposures included in *Consequence Analytic Tools for NBC Operations* with the published Saslaw data, the authors were able to identify the two cases excluded from the latter but included in *Consequence Analytic Tools for NBC Operations*. These involve exposures of 10 and 17 organisms, both of which failed to induce illness. If these cases are added to the published Saslaw data set, the authors were then able to derive an ID_{50} of 10 organisms and a probit slope of 1.90 probits per logarithm of dose.

Pending access to the unpublished case data and assuming that these data will match those described in *Consequence Analytic Tools for NBC Operations*, the authors recommend modeling tularemia infectivity as a lognormal distribution with an ID_{50} of 10 organisms and a probit slope of 1.90 probits per logarithm of dose. This distribution has a mean of 2.30 and a standard deviation of 1.69.

The CDF of the lognormal distribution that corresponds to these data and used to model the aerosol infectivity of *F. tularensis* in humans is:

$$F(d) = \frac{1}{2} + \frac{1}{2}\text{erf}\left[\frac{\ln(d) - \mu}{\sigma\sqrt{2}}\right]$$

where:

F is the cumulative fraction of persons who have become infected with tularemia,

d is the infective dose [organisms],

μ is the mean of the variable's natural logarithm [= $\ln(ID_{50})$ = ln(10 organisms) =2.30],

m is the probit slope [= 1.90 probits/log(dose)],

σ is the standard deviation of the variable's natural logarithm [= $e^{1/m}$ = $e^{1/1.90}$ = 1.69], and

erf is the error function where $\text{erf}(x) = \frac{2}{\sqrt{\pi}}\int_0^x e^{-t^2}\,dt$.

[225] Anno and Deverill et al., *Consequence Analytic Tools for NBC Operations*, 18–19.

The proposed tularemia infectivity model is shown graphically in Figure 14 below.

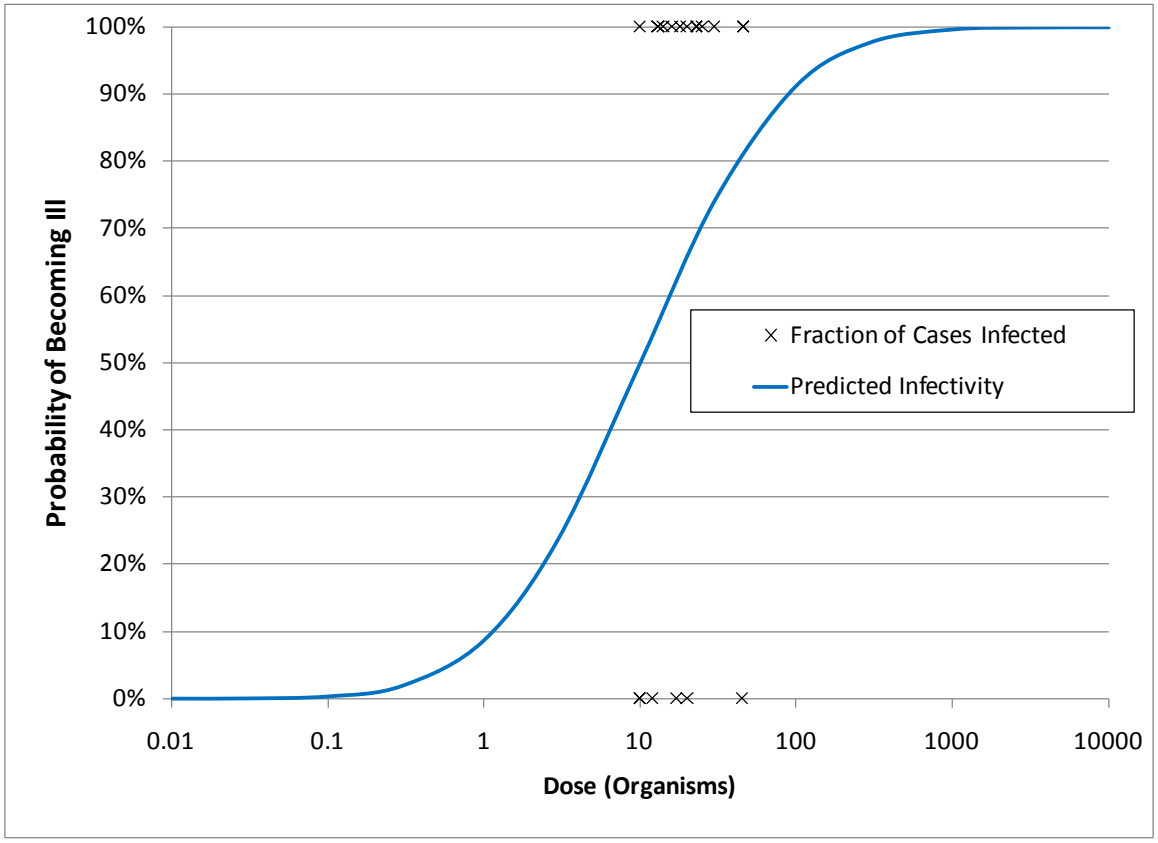

Figure 14. Tularemia Infectivity

D. Lethality

Today tularemia is readily treated with antibiotics and deaths from the disease are extremely rare. Prior to antibiotic use, however, lethality was high. *Medical Aspects of Biological Warfare* provides a range of 5% to 57%, depending on type of infection,[226] while the *JAMA Consensus Statement on Tularemia* reports that mortality rates were in the range of 5% to 15% overall, but 30% to 60% for pneumonic and severe systemic forms of the disease.[227]

The *AMedP-8 (Biological) Methods Report* states that the mortality rate for untreated pneumonic treatment is 30% to 40%,[228] citing *Consequence Analytic Tools for NBC Operations*, which in turn references personal communications from subject matter

[226] Hepburn, Friedlander, and Dembek, "Tularemia," in *Medical Aspects of Biological Warfare*, 168.

[227] Dennis et al., "Tularemia as a Biological Weapon: Medical and Public Health Management," 2767.

[228] Anno et al., *AMedP-8 (Biological) Methods Report*, 80.

experts for this value.[229] The *AMedP-8 (Biological) Methods Report* combines a postulated constant daily lethality rate with a dose-dependent duration of fever model (see below) to result in a dose-dependent model of lethality. By assigning a value of 3% to the daily lethality rate, the *AMedP-8 (Biological) Methods Report* was able to generate an overall lethality rate of 20% to 50%, depending on dose.[230]

Both *Medical Aspects of Biological Warfare* and the *JAMA Consensus Statement on Tularemia* cite a study by Stuart and Pullen,[231] published in 1945, in which the authors reviewed available literature on pneumonic tularemia and reported on additional pneumonic cases they had personally managed at Charity Hospital in New Orleans, Louisiana. These same authors separately published an analysis of 225 tularemia cases of all types seen at Charity Hospital from 1928 through 1944.[232]

Of the 225 cases of tularemia observed by Stuart and Pullen, only 14 were of the typhoidal form (about 6% overall); the remainder were ulceroglandular (80%), oculoglandular (3%), and glandular (10%). There were 17 deaths among these cases, for an overall lethality rate of about 8%. The lethality rate varied by type of infection, however; the rate among typhoidal patients was 50%, while the rate among all other types of tularemia infection was less than 5%. Of those who died, 15 of 17 had pneumonia listed as a presumptive cause of death.[233]

Stuart and Pullen's literature review considered 268 cases of pneumonic tularemia resulting in 107 deaths, a lethality rate of 40%.[234] These cases include pneumonias that developed among tularemia cases of all types; for those reported in the literature, Stuart and Pullen do not categorize lethality rates by type of tularemia. However, they do note that in their literature review, the reported symptoms of patients with pneumonic tularemia fall into two general groups, with those experienced by typhoidal patients being distinctly different than those experienced by patients with ulceroglandular, glandular, or oculoglandular tularemia.[235]

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[229] Anno and Deverill et al., *Consequence Analytic Tools for NBC Operations*, 16. This document footnotes additional sources describing lethality rates as high as 60% for tularemia in its more severe forms. See for example L. Foshay, "Diagnosis and Treatment of Tularemia," *Postgraduate Medicine* 4, No. 4 (October 1948).

[230] Anno et al., *AMedP-8 (Biological) Methods Report*, 78–80.

[231] Byron M. Stuart and Roscoe L. Pullen, "Tularemic Pneumonia: Review of American Literature and Report of 15 Additional Cases," *American Journal of Medical Science* 210 (1945): 223–36.

[232] Roscoe L. Pullen and Byron M. Stuart, "Tularemia: Analysis of 225 Cases," *Journal of the American Medical Association* 129 no. 7 (1945): 495–500.

[233] Ibid., 500.

[234] Stuart and Pullen, "Tularemic Pneumonia: Review of American Literature and Report of 15 Additional Cases," 231.

[235] Ibid., 227.

The Stuart and Pullen study provides data on type of tularemia for the 21 cases of pneumonia among tularemia patients they personally observed at Charity Hospital; among these, there were 12 deaths, for an overall lethality rate of 57% among pneumonic cases of tularemia.[236] All of these cases were either of the ulceroglandular or typhoidal forms; lethality rates were 46% for ulceroglandular patients (6 of 13) and 75% for typhoidal patients (6 of 8).

The literature in general suggests that among historical cases, lethality rates were higher for typhoidal tularemia patients than for patients with other forms of tularemia—around 50%--and for tularemia patients of all forms who developed pneumonia—around 40%. Stuart and Pullen do not describe the extent of overlap in these categories among reported cases, but in the cases they observed that were both pneumonic and typhoidal, the lethality rate was significantly higher, at 75%. Because the authors believe that data from historical cases of typhoidal tularemia with pneumonia provide the best surrogate data for untreated tularemia acquired via inhalation, they recommend modeling tularemia lethality with a case fatality rate of 75%, as observed in the Stuart and Pullen study.

E. Incubation Period

The incubation period for pneumonic tularemia acquired via inhalation is rarely discussed in clinical studies of the disease. Unless the exposure is controlled, as in the case of the vaccine challenge studies, or is the result of a laboratory accident, it is difficult to know exactly when exposure occurred. The *JAMA Consensus Statement on Tularemia* states, without attribution, that the incubation period for tularemia acquired via inhalation ranges from 1 to 14 days, with most cases occurring 3 to 5 days after exposure.[237]

Using the unpublished MRV case data, the authors of *Consequence Analytic Tools for NBC Operations* found that incubation period was highly correlated with challenge dose. They derived the relationship between the logarithm of dose and incubation period using a regression model of the form:

$$t_0 = \alpha + \beta \log N_0$$

[236] Three of the deaths reported by Stuart and Pullen (Pullen and Stuart, "Tularemia: Analysis of 225 Cases") listing pneumonia as a presumptive cause of death were excluded from the reported pneumonic cases (Stuart and Pullen, "Tularemic Pneumonia") because they did not meet their criteria for diagnosis of tularemia. These criteria included 1) autopsy with recovery of the organism from culture or animal inoculation; 2) aspiration biopsy of the lung with recovery of the organism from culture or animal inoculation; and 3) positive physical signs of pneumonic consolidation with x-ray confirmation and rising blood agglutination titers for the organism (Stuart and Pullen, "Tularemic Pneumonia: Review of American Literature and Report of 15 Additional Cases," 232). None of the excluded cases was typhoidal.

[237] Dennis et al., "Tularemia as a Biological Weapon: Medical and Public Health Management," 2765.

where:

t_0 = time to onset of infection (days),

N_0 = dose (organisms inhaled),

$\alpha = 6.5380$, and

$\beta = -0.8207$.[238]

Extrapolation to a single organism results in an onset time of about 6.5 days. In consultation with subject matter experts, *Consequence Analytic Tools for NBC Operations* also established a minimum onset time of 1.5 days in cases of very high doses, those in excess of 10^7 organisms.[239] For doses in the range of 10^5 to 10^7 organisms, the authors proposed a logarithmic/quadratic relationship of the following form, based on solution and slope matching with Equation 2 above:

$$t_0(N_0) = \alpha_0 + \alpha_1 \log N_0 + \alpha_2 (\log N_0)^2$$

where:

t_0 = time to onset of infection (days), and

N_0 = dose (organisms inhaled).

$\alpha_0 = 10.9563$,

$\alpha_1 = -2.5886$, and

$\alpha_2 = 0.1763$.[240]

Thus in the model described in *Consequence Analytic Tools for NBC Operations*, the range of onset times for tularemia is bounded at 1.5 and 6.5 days.

The data set used in *Consequence Analytic Tools for NBC Operations*, as noted, included the 16 cases of positive response described in the Saslaw vaccine respiratory challenge study as well as 96 other cases described in the set of unpublished MRV data. These latter cases were all exposed to higher challenge doses than those in the Saslaw study, ranging from 315 to 62,000 organisms.

The published Saslaw data includes values for incubation periods for positive responses. Table 47 provides dose and observed incubation period from the Saslaw study, and provides an incubation period estimated from dose using the model in *Consequence Analytic Tools for NBC Operations*. As can be seen from the observed data, there is indeed a tendency for incubation period to be shorter given a higher dose. Although the range of observed incubation periods is greater than that seen in the predicted incubation

[238] Ibid., 28–9.

[239] Ibid., 30.

[240] Ibid., 31.

period, the authors found the results of the *Consequence Analytic Tools for NBC Operations* model to be reasonable: the Saslaw data set is small relative to that used in *Consequence Analytic Tools for NBC Operations*, and the small challenge doses likely fall in the tail of the distribution, where greater variance would be expected. Therefore they recommend continued use of the *Consequence Analytic Tools for NBC Operations* model to estimate time of onset; this model, with its upper and lower bounds, is portrayed graphically in Figure 15.

Table 47. Tularemia Incubation Period Observed from Saslaw Data[241]

Individual Dose (Organisms)	Observed Incubation Period (Days)	*Consequence Analytic Tools for NBC Operations* Predicted Incubation Period (Days)
10	6	5.7
14	5	5.6
15	6	5.6
16	6	5.5
18	5	5.5
18	7	5.5
20	7	5.5
23	6	5.4
23	6	5.4
25	5	5.4
30	5	5.3
46	4	5.2
46	4	5.2
48	5	5.2
50	4	5.1
52	5	5.1

[241] Saslaw et al., "Tularemia Vaccine Study, II: Respiratory Challenge," 705, 708.

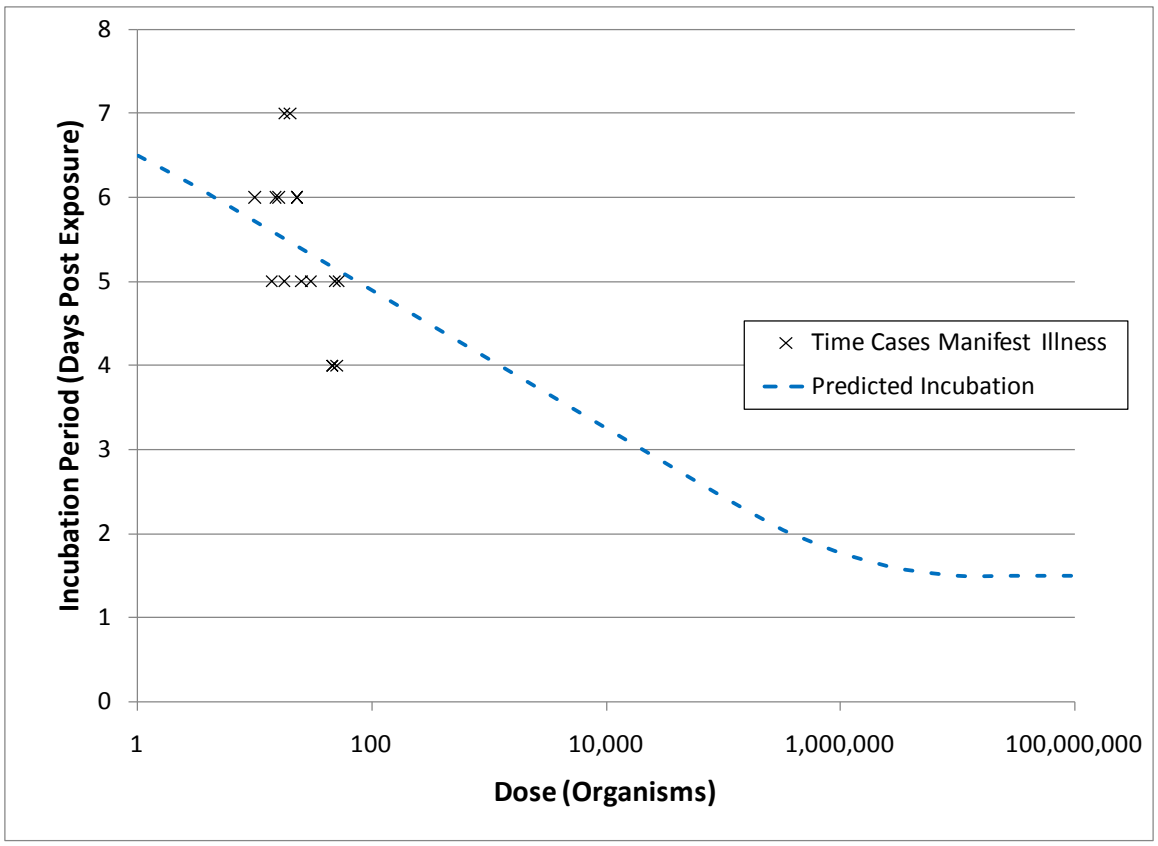

Figure 15. Tularemia Bounded Dose-Dependent Incubation Period

F. Illness Profile

Tularemia initially presents as a sudden, acute, non-specific febrile illness, and is very difficult to diagnose if not of the ulceroglandular or oculoglandular forms. Even in its initial stage, the disease is generally severe; the *JAMA Consensus Statement on Tularemia* notes that many of the MRVs exposed to aerosol challenge were incapacitated in the first one or two days of illness.[242] Recovery from tularemia is generally described as slow. *Medical Aspects of Biological Warfare* states that "untreated tularemia patients usually have a prolonged illness lasting for months." Francis observed that convalescence typically took several weeks—in rare cases as long as a year—during which time patients were extremely weak and had limited endurance.[243]

In the Saslaw study, control subjects who had a positive response to respiratory challenge experienced fever, myalgia, headache, anorexia, and dry non-productive cough.

[242] Dennis et al., "Tularemia as a Biological Weapon: Medical and Public Health Management," 2767.

[243] Francis, "Tularemia," 1247.

Substernal tightness and pain were common, and chills occasionally observed.[244] Subjects were given antibiotics within a day or two of symptom onset and all recovered quickly; none showed pulmonary abnormalities on X-rays prior to the initiation of therapy.

McCrumb described the initial clinical signs and symptoms observed among eight vaccine study control subjects exposed to respiratory challenges of 200 to 20,000 organisms.[245] All controls developed disease characterized by abrupt onset of fever, headache, chills and sore throat, accompanies by malaise, myalgia and backache. Fevers were very high, between 103° and 104° F. All patients also had cough and most experienced chest pain, either sharp pleural pain aggravated by breathing or oppressive substernal pain. X-rays showed a small, discrete pulmonary lesion in two patients.

As described, Stuart and Pullen identified a distinct clinical presentation in typhoidal tularemia patients with pneumonia.[246] They observed sudden onset of fever, chills, shortness of breath, cough, chest pain, and profuse sweating. Patients appeared extremely ill and were frequently suspected of having typhoid fever. They also observed that pulmonary symptoms were less severe than those associated with other forms of pneumonia, and symptoms of bronchitis are usually present before pneumonia is recognized. Once pneumonia manifests, it can rapidly become severe, leading to respiratory failure and death. In severe cases, Stuart and Pullen observed elevated pulse, rapid and shallow breathing, confusion, delirium, and even coma.

The illness profile submodel characterizes disease by the stages of its clinical course, the signs and symptoms present within each stage, and the overall severity of illness, using the scale described in Table 1. The authors recommend that the illness profile for tularemia comprise three stages, two for both survivors and non-survivors, and a third for survivors representing the recovery period.

Stage 1 of pneumonic tularemia encompasses the initial febrile period of the disease, marked by high fever, headache, chills, sore throat, myalgia, and chest pain. Onset is sudden, and patients in this phase of the disease appear severely ill and can be incapacitated. Consequently, this stage should be characterized as Severity Level 3.

Stage 2 of pneumonic tularemia begins with the onset of pneumonia. Signs and symptoms from Stage 1 continue, with the addition of respiratory distress. Non-survivors

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[244] Ibid., 713.

[245] McCrumb, "Aerosol Infection of Man with *Pasteurella Tularensis*," 264. The McCrumb article does not provide the type of dose, response, and time of onset data included in the Saslaw study, although Anno and Deverill include the McCrumb data in the set of unpublished MRV data they used in the development of their model.

[246] Stuart and Pullen, "Tularemic Pneumonia: Review of American Literature and Report of 15 Additional Cases," 227.

would experience respiratory distress and ultimately respiratory failure in this stage, which would end in death. The pulmonary symptoms experienced by survivors would be milder in this stage than for non-survivors, and the stage would end with the resolution of pneumonia. For non-survivors, Stage 2 would be characterized as Severity Level 4, while survivors Stage 2 would be characterized as Severity Level 3.

Stage 3 of pneumonic tularemia is considered for survivors only, and is used to represent recovery from the disease. Convalescence is protracted and is marked by severe weakness. Because patients would not be expected to resume normal activity in this period, it is characterized as Severity Level 2.

The proposed illness profile for pneumonic tularemia is summarized in Table 48.

Table 48. Illness Profile for Pneumonic Tularemia

	Stage 1 (all)	Stage 2 (non-survivors)	Stage 2 (survivors)	Stage 3 (survivors)
Signs and Symptoms (S/S)	High fever, headache, chills, sore throat, myalgia, chest pain	Stage 1 S/S plus severe pneumonia, respiratory distress	Stage 1 S/S plus mild pneumonia	Malaise, severe weakness
S/S Severity	Severity Level 3 ("Severe")	Severity Level 4 ("Very Severe")	Severity Level 3 ("Severe")	Severity Level 2 ("Moderate")
Outlook	Individual will progress to Stage 2	Death	Individual will progress to Stage 3	Recovery

G. Duration of Illness

Today, tularemia is readily treated with antibiotics. In the tularemia vaccine challenge studies conducted with human volunteers, for example, all subjects who developed disease were administered antibiotics and in all cases the progression of disease was arrested. Development of the duration of illness submodel for tularemia must therefore rely on data from historical cases of tularemia prior to the antibiotic era. Once again, preference is given to data on cases of typhoidal tularemia with pneumonia.

Medical Aspects of Biological Warfare states that "untreated tularemia patients usually have a prolonged illness lasting for months,"[247] and the *JAMA Consensus Statement on Tularemia* notes that in untreated tularemia, "symptoms often persist for several weeks and, sometimes, for months, usually with progressive debility."[248] Neither

[247] Hepburn, Friedlander, and Dembek, "Tularemia," in *Medical Aspects of Biological Warfare*, 173.

[248] Dennis et al., "Tularemia as a Biological Weapon: Medical and Public Health Management," 2767.

reference differentiates among clinical form of the disease or provides any greater detail than that cited.

In *Consequence Analytic Tools for NBC Operations*, the authors used two historical cases of tularemia for which body temperature was recorded[249] as the basis for developing a dose-dependent duration of illness model. In one case, the febrile period lasted for 16 days, in the second, it lasted for 23 days. The authors further postulated that because the first case was significantly less severe and of shorter duration than the second, these two cases could be used as a "reasonable paradigm for high and low dose response."[250] Using the recorded temperature data for the two cases and a linear function developed from MRV data to describe time to near-maximum body temperature,[251] the authors calculated estimated doses for the first case of 10 organisms, and for the second case of 44,063 organisms.[252] These estimated doses and durations of fever were then used to derive a model of duration of fever as a function of dose; this model was then qualified by limiting the febrile period to 30 days, as a result of consultation with subject matter experts.

The authors of *Consequence Analytic Tools for NBC Operations* were limited in their choice of historical case data on which to base their calculations by their focus on fever and its relationship to performance, and the corresponding value of case records that described body temperature measurements over time. In the present study, such restrictions and incentives do not exist, allowing use of a broader set of case data.

Stuart and Pullen's clinical study of pneumonic tularemia patients at Charity Hospital described the duration of illness before and after pneumonia was confirmed via chest x-rays. The information on typhoidal patients provided in that study is summarized in Table 49.

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[249] W. A. Simpson, *Tularemia History, Pathology, Diagnosis, and Treatment* (New York, NY: Paul B. Hoeber, Inc., 1929), referenced in Anno and Deverill et al., *Consequence Analytic Tools for NBC Operations*, 33.

[250] Anno and Deverill et al., *Consequence Analytic Tools for NBC Operations*, 33.

[251] This linear function is of the same form and developed from the same set of MRV data as that used to describe incubation period in *Consequence Analytic Tools for NBC Operations*.

[252] Anno and Deverill et al., *Consequence Analytic Tools for NBC Operations*, Table 2–3.

Table 49. Duration of Illness Data for Typhoidal Tularemia Patients with Pneumonia[253]

Case	Duration of Symptoms Before Pneumonia (Days)	Duration of Pneumonia (days)	Total Duration of Illness
Survivor #1	14	33	47
Survivor #2	10	22	32
Survivor Average	***12***	***28***	***40***
Fatality #1	10	5	15
Fatality #2	6	4	15
Fatality #3*	8	2	10
Fatality #4	8	2	10
Fatality #5	12	5	10
Fatality #6	9	19	17
Fatality Average	***9***	***6***	***15***

* Duration of symptoms before pneumonia for this case was omitted from Stuart and Pullen, "Tularemic Pneumonia," but derived by cross-referencing data on deaths from tularemia provided in Pullen and Stuart, "Tularemia: Analysis of 225 Cases."

Although the numbers of cases are small for both survivors and non-survivors, among them the survivors had a clearly different duration of illness, particularly in the duration of pneumonia. The authors propose to use these data to assign duration to various stages of illness described in the pneumonic tularemia illness profile for survivors and non-survivors. However, because the numbers of cases were so small, no attempt has been made to derive a model in any functional form from the data; rather, the authors propose to use the average values to populate the duration submodel.

For the period of convalescence described by Stage 3 of the illness profile, described in various sources as "prolonged" and "weeks to months," the authors propose to use a constant value of 12 weeks.

The proposed duration of each stage of pneumonic tularemia is summarized in Table 50.

Table 50. Pneumonic Tularemia Duration of Illness

	Stage 1	Stage 2	Stage 3
Survivors	12 days	28 days	12 weeks
Non-survivors	9 days	6 days	

[253] Stuart and Pullen, "Tularemic Pneumonia: Review of American Literature and Report of 15 Additional Cases," 233.

H. Medical Countermeasures and Treatment

As noted elsewhere in this chapter, antibiotics have proven effective in the treatment of tularemia resulting from respiratory exposure. Since the advent of antibiotic therapy, overall case fatality rates for tularemia have fallen to 1 to 2.5%[254] and all of the MRVs who had a positive response to respiratory challenge with tularemia recovered rapidly after beginning antibiotic therapy. Both *Medical Aspects of Biological Warfare*[255] and the *JAMA Consensus Statement on Tularemia*[256] make extensive recommendations on the use of antibiotics for treatment of tularemia.

Another study of MRVs assessed the effectiveness of antibiotics in preventing onset of disease following exposure.[257] In this study, 34 subjects were exposed to a respiratory challenge of 25,000 organisms and given tetracycline as a prophylaxis, in varying doses and for varying periods of time. Table 51 provides information on the antibiotic regimens tested in the study and their outcome.

Table 51.Tetracycline Prophylaxis of Human Airborne Tularemia[258]

Daily Dose* (g)	Frequency	Duration (days)	No. of Subjects	No. Ill During Treatment	No. Ill After Treatment
1	Daily	15	10	0	2
1	Daily	28	8	0	0
2	Daily	14	8	0	0
1	Every 2nd Day	19	8	2	8

*Divided into morning and evening doses.

All subjects who developed the disease during or after the period of prophylaxis were subsequently treated with streptomycin; all recovered quickly and without complications.

The study concluded that antibiotics could successfully be used to prevent onset of illness following respiratory challenge with tularemia, provided they were administered in sufficient amounts to suppress growth of intracellular organisms, and provided they were administered for a sufficient period of time.[259]

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[254] Hepburn, Friedlander, and Dembek, "Tularemia," in *Medical Aspects of Biological Warfare*, 175.

[255] Ibid., 176.

[256] Dennis et al., "Tularemia as a Biological Weapon: Medical and Public Health Management," 2770, Table 3.

[257] William D. Sawyer et al., "Antibiotic Prophylaxis and Therapy of Airborne Tularemia." *Bacteriological Reviews* 20, no. 3 (1966): 542–48.

[258] Ibid., 545. This table is a replica of the one provided in the study.

[259] Ibid., 547.

The *JAMA Consensus Statement on Tularemia*[260] recommends that individuals who are suspected of being exposed to tularemia be given doxycycline or ciprofloxacin orally for 14 days as prophylaxis.

I. Summary and Conclusions

The parameters described in this chapter were derived from a collection of articles which include analyses of controlled human exposures to tularemia, as well as analyses of cases, outbreaks, and the microbiological characteristics of tularemia. The controlled human exposure data, however, was never completely published, and leads to some inconsistencies between this study and previous analyses. It is the recommendation of the authors to use the parameters described above, but that the complete controlled human exposure data be collated and published to allow for a thorough analysis to derive the human response parameters of interest. Once that is complete, it may be of value to then pursue a research program to further quantitatively characterize the infectivity, lethality, incubation, duration, and course of illness of tularemia.

Based on the available data, analysis and literature review as described in the preceding sections, the authors recommend using the parameter values provided in Table 52 to model the pneumonic form of tularemia. The illness profile for pneumonic tularemia, provided in Section F, is repeated in Table 53.

[260] Dennis et al., "Tularemia as a Biological Weapon: Medical and Public Health Management," 2771.

Table 52. Pneumonic Tularemia Model Parameters Summary Table

Submodel	Type	Parameters
Infectivity	Lognormal distribution	ID_{50} = 10 organisms Probit slope = 1.90 probits/log(dose)
Lethality	Rate	75%
Incubation period	For doses $<10^5$ organisms:	
	Log-linear function	$\alpha = 6.54$, $\beta = -0.821$
	For doses 10^5 to 10^7 organisms:	
	Log-quadratic function	$\alpha_0 = 11.0$; $\alpha_1 = -2.59$; $\alpha_1 = 0.176$
	For doses $> 10^7$ organisms:	
	Constant	1.5 days
Duration of illness (non-survivor)		
• Stage 1	Constant	9 days
• Stage 2	Constant	6 days
Duration of illness (survivor)		
• Stage 1	Constant	12 days
• Stage 2	Constant	28 days
• Stage 3	Constant	12 weeks

Table 53. Illness Profile for Pneumonic Tularemia

	Stage 1 (all)	Stage 2 (non-survivors)	Stage 2 (survivors)	Stage 3 (survivors)
Signs and Symptoms (S/S)	High fever, headache, chills, sore throat, myalgia, chest pain	Stage 1 S/S plus severe pneumonia, respiratory distress	Stage 1 S/S plus mild pneumonia	Malaise, severe weakness
S/S Severity	Severity Level 3 (“Severe”)	Severity Level 4 (“Very Severe”)	Severity Level 3 (“Severe”)	Severity Level 2 (“Moderate”)
Outlook	Individual will progress to Stage 2	Death	Individual will progress to Stage 3	Recovery

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Appendix A
Clinical Descriptions of Nine Cases of Accidental SEB Exposure (excerpted from Sidell 1965)

H.D. (Figure A-1) This 49-year-old Caucasian, male, animal caretaker was admitted to the hospital at 1930 hours on the day of exposure. His first objective symptoms of illness began about 1600 hours with a shaken chill, headache, and weakness. Shortly thereafter he developed myalgia and nausea with vomiting. In retrospect, the patient stated that he had noted a "grabbing" sensation under his sternum and cough during the afternoon exposure period. On admission his temperature was 103.8F, the pulse rate 114, and the blood pressure normal. Significant physical findings were limited to the chest. He was tachypneic and during the examination became quite dyspneic. Inspiratory rales were present in the left lung base. His temperature rose to 106F within four hours of admission but responded to aspirin and sponging. He gradually defervesced and became afebrile by the seventh hospital day. Dyspnea became worse during the first few hours after admission when diffuse expiratory as well as inspiratory rales were heard bilaterally. Partial relief of dyspnea occurred after administration of amirophyllin suppository. Exertional dyspnea was present during the next 48 hours; rales persisted for approximately nine days. The patient's main complaint during hospitalization was a persistent nonproductive cough which continued despite treatment with expectorants, anti-tussive drugs, and cool mist, but gradually improved over a two to three week period. Nausea, anorexia, malaise, myalgia, and headache were other prominent symptoms during the first three days of illness. He was discharged on the seventh hospital day asymptomatic except for a nonproductive cough.

Chest x-ray on the night of admission revealed accentuation of peribronchial markings with a patchy area of increased density in the left mid-lung field compatible with an area of pulmonary edema. On a film taken three hours after admission the density in the left mid-lung field had increased and Kerley lines, indicative of interstitial edema were present in both lower lung fields. The film taken two days after admission revealed improvement of the larger density but discoid atelectasis was present in the left base. The chest x-ray taken at the time of discharge was within normal limits.

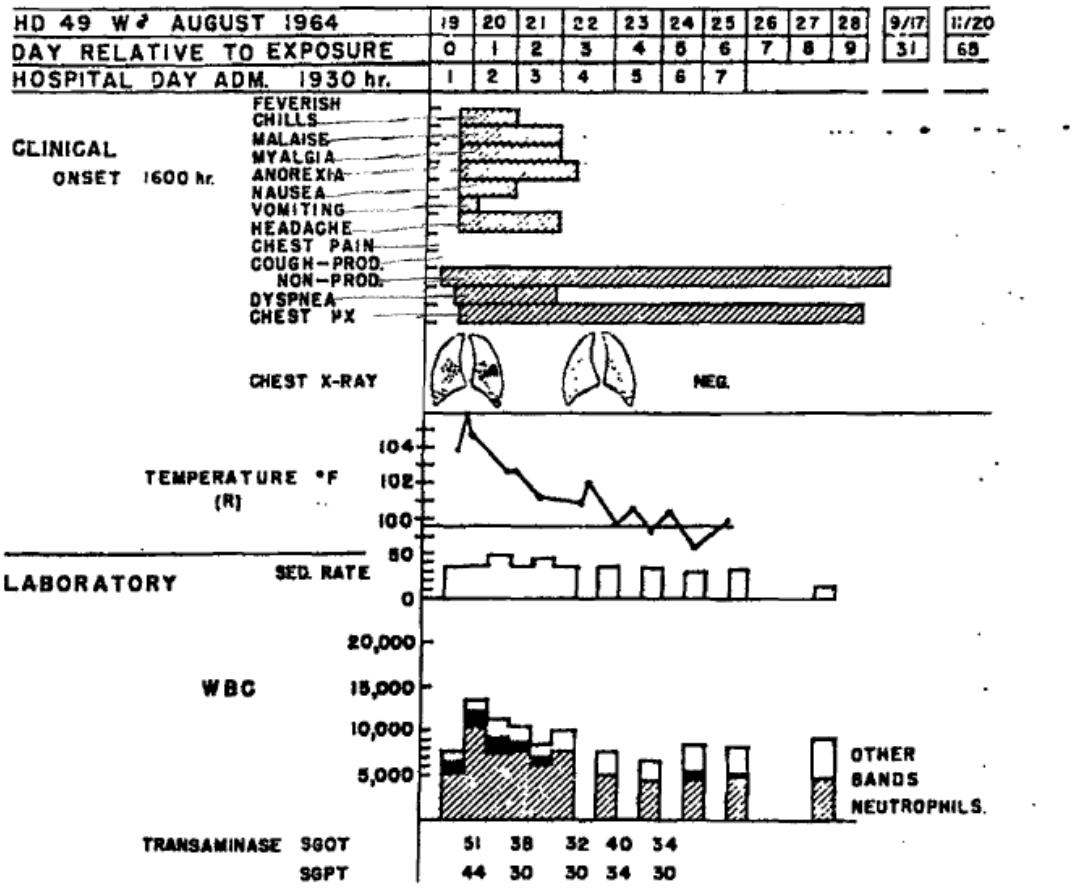

Figure A-1. Case Report 1, HD

Table A-1. Derived Latent Period and Duration of Symptoms, Case Report 1 HD

	Case #1 (HD)			
	Onset (Date/Time)	**Completion (Date/Time)**	**Latent Period* (hrs)**	**Duration (hrs)**
Hospitalization	8/19/64 19:30	8/26/64 12:00	10.5	160.5
Clinical Onset	8/19/64 16:00	(N/A)	7	
Feverish	(Not Reported)			
Chills	8/19/64 16:00	8/21/64 0:00	7	32
Malaise	8/19/64 16:00	8/22/64 0:00	7	56
Myalgia	8/19/64 16:00	8/22/64 0:00	7	56
Anorexia	8/19/64 16:00	8/22/64 12:00	7	68
Nausea	8/19/64 16:00	8/21/64 0:00	7	32
Vomiting	8/19/64 16:00	8/20/64 4:00	7	12
Headache	8/19/64 16:00	8/22/64 0:00	7	56
Chest Pain	(Not Reported)			
Cough - Productive	(Not Reported)			
Cough - Nonproductive	8/19/64 13:00	9/10/64 0:00	4	515
Dyspnea	8/19/64 16:00	8/22/64 0:00	7	56
Chest Px	8/19/64 18:00	8/29/64 0:00	9	222
Elevated Temp	8/19/64 19:30	8/25/64 0:00	10.5	124.5

*Relative to assumed exposure time of 09:00 hours on 8/19/64 (start of first presumed exposure period).

B.A. (Figure A-2) This 37-year-old Caucasian, male, animal care taker was admitted at 2030 hours on the day of exposure. About two hours prior to admission he developed a mild shaking chill and malaise followed by dyspnea with substernal chest tightness, nonproductive cough, myalgia, and a sore throat. He felt nauseated and had one loose bowel movement but without associated abdominal pain or vomiting. In retrospect, the patient recalled a moderate frontal headache, dizziness, and burning of the eyes during the afternoon exposure. Other than a temperature of 101.6F the physical examination on admission was normal. The patient's temperature rose to 104.4F three hours after admission and then gradually fell to normal over the next three day period. Symptomatically the patient improved after 24 hours but continued to be troubled by a nonproductive cough and some anterior chest pain on coughing. The cough gradually responded to expectorants and anti-tussive drugs, he was discharged on the sixth hospital day. The chest x-ray on admission showed pulmonary interstitial edema. On the film taken the day after admission discoid atelectasis was seen in the left base but there was no edema. On the fourth hospital day, there was clearing of the atelectasis, and by the fifth hospital day, the chest x-ray was negative.

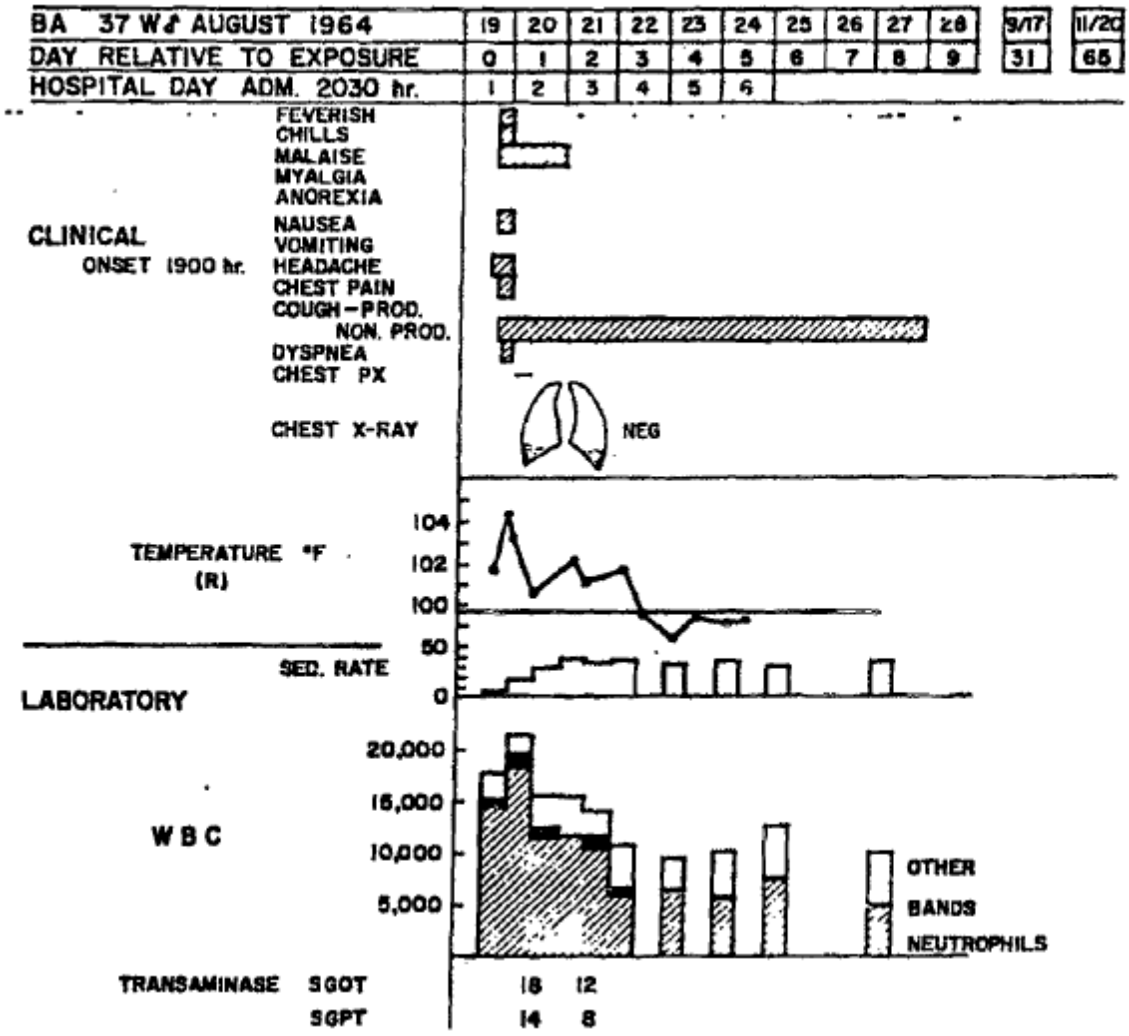

Figure A-2. Case Report 2, BA

Table A-2. Derived Latent Period and Duration of Symptoms, Case Report 2, BA

	Case #2 (BA)			
	Onset (Date/Time)	**Completion (Date/Time)**	**Latent Period* (hrs)**	**Duration (hrs)**
Hospitalization	8/19/64 20:30	8/25/64 12:00	11.5	135.5
Clinical Onset	8/19/64 19:00	(N/A)	10	
Feverish	8/19/64 19:00	8/20/64 0:00	10	5
Chills	8/19/64 19:00	8/20/64 0:00	10	5
Malaise	8/19/64 19:00	8/21/64 0:00	10	29
Myalgia	(Not Reported)			
Anorexia	(Not Reported)			
Nausea	8/19/64 19:00	8/20/64 0:00	10	5
Vomiting	(Not Reported)			
Headache	8/19/64 14:00	8/20/64 0:00	5	10
Chest Pain	8/19/64 19:00	8/20/64 0:00	10	5
Cough - Productive	(Not Reported)			
Cough - Nonproductive	8/19/64 19:00	8/28/64 20:00	10	217
Dyspnea	8/19/64 20:30	8/20/64 0:00	11.5	3.5
Chest Px	(Not Reported)			
Elevated Temp	8/19/64 20:30	8/22/64 12:00	11.5	63.5

*Relative to assumed exposure time of 09:00 hours on 8/19/64 (start of first presumed exposure period).

M.H.D. (Figure A-3) This 24-year-old Caucasian, Lieutenant, veterinarian was admitted at 1930 hours on the day of exposure. About two hours prior to admission the patient suddenly developed shortness of breath, substerna pleuritic chest pain, paroxysmal cough productive of a small amount of clear sputum and a shaking chill, but he had noted a “raw” sensation in his chest along with headache, nausea and some abdominal cramps shortly after beginning the morning exposure. Because of these symptoms he had left work about one hour earlier than usual. On admission, his temperature was 102.8F; His significant physical findings were limited to the chest. He had moderate dyspnea on slight exertion such as when talking, and orthopnea. Fine inspiratory rales were present at the right base but there was no dullness to percussion. Within a few hours of admission his temperature spiked to a peak of 104.6F and remained between 102–104F for 48 hours, after which it returned to normal over a three day period. Dyspnea progressed during the first few hours after admission but overt evidence of congestive heart failure was absent. The dyspnea was much improved after the first 12 hours of hospitalization and gradually disappeared over the next 24 hours. However, the patient had frequent severe paroxysms of cough, as well as wretching and vomiting which were relieved by parenteral Compazine. On the day following admission, no rales were audible. The nonproductive cough continued but gradually improved over the next two weeks. He was discharged on the eighth hospital day, completely asymptomatic except for a non-productive cough. The chest x-ray on admission showed accentuation of the peribronchial markings in both lung fields. On the third and fourth hospital days, the chest x-ray showed areas of discord atelectasis in the bases. The chest x-ray was normal by the fifth hospital day. Chest x-ray taken day 13 post exposure is shown.

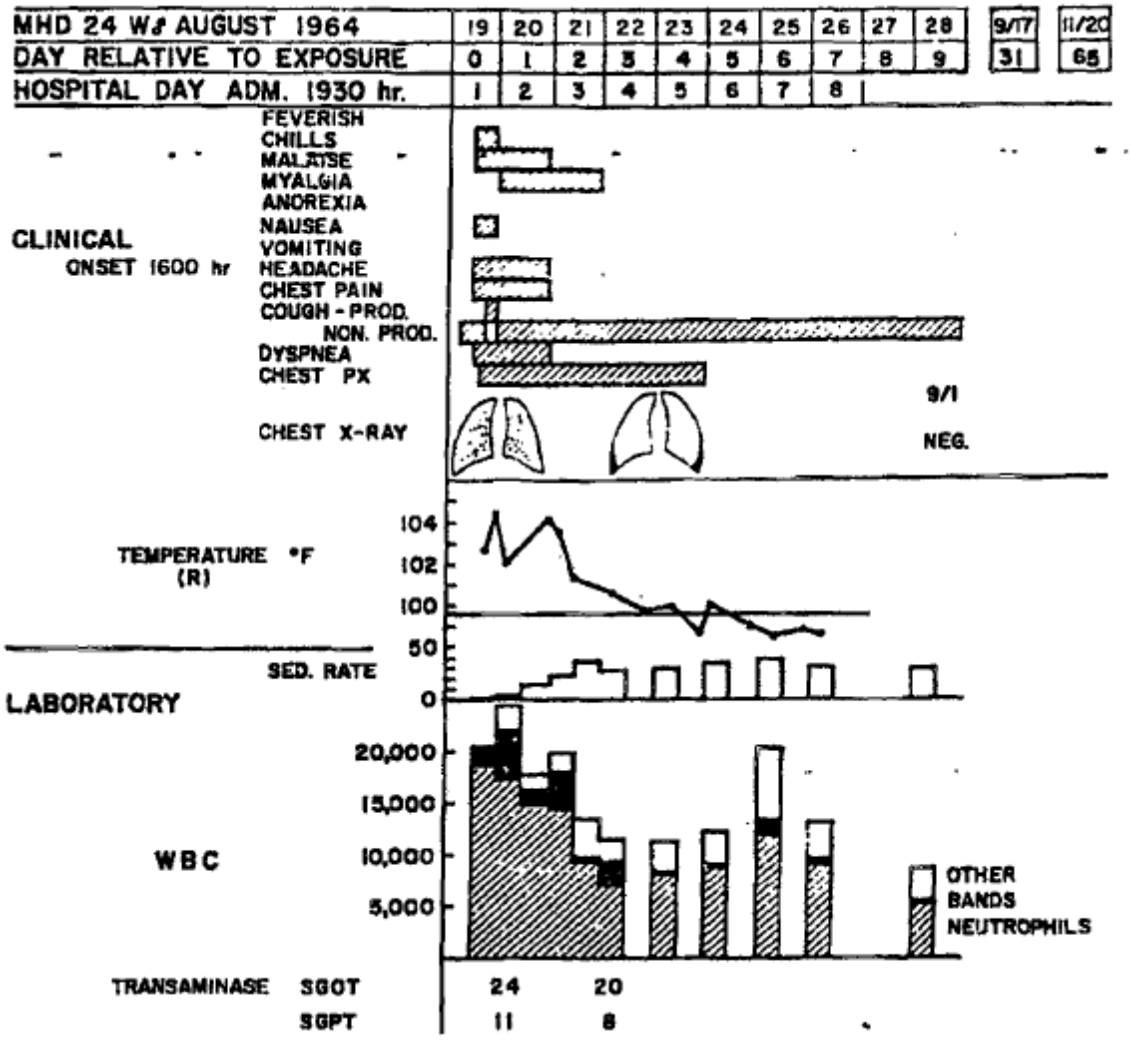

Figure A-3. Case Report 3, MHD

Table A-3. Derived Latent Period and Duration of Symptoms, Case Report 3, MHD

	Case #3 (MHD)			
	Onset (Date/Time)	**Completion (Date/Time)**	**Latent Period* (hrs)**	**Duration (hrs)**
Hospitalization	8/19/64 19:30	8/27/64 12:00	10.5	184.5
Clinical Onset	8/19/64 16:00	(N/A)	7	
Feverish	(Not Reported)			
Chills	8/19/64 16:00	8/20/64 0:00	7	8
Malaise	8/19/64 16:00	8/21/64 0:00	7	32
Myalgia	8/20/64 0:00	8/21/64 19:30	15	43.5
Anorexia	(Not Reported)			
Nausea	8/19/64 16:00	8/20/64 0:00	7	8
Vomiting	(Not Reported)			
Headache	8/19/64 16:00	8/21/64 0:00	7	32
Chest Pain	8/19/64 16:00	8/20/64 0:00	7	8
Cough - Productive	8/19/64 20:00	8/20/64 0:00	11	4
Cough - Nonproductive	8/19/64 10:00	9/1/64 19:30	1	321.5
Dyspnea	8/19/64 16:00	8/21/64 0:00	7	32
Chest Px	8/19/64 18:00	8/24/64 0:00	9	102
Elevated Temp	8/19/64 19:30	8/23/64 0:00	10.5	76.5

*Relative to assumed exposure time of 09:00 hours on 8/19/64 (start of first presumed exposure period).

R.F.J. (Figure A-4) This 49-year-old Caucasian, male, microbiologist was admitted at 2030 hours on the day of exposure. He was well until 1600 hours when he first developed a nonproductive cough and mild sub-sternal chest pain. At 1800 hours, he noticed dyspnea on mild exercise, myalgia and headache. On admit, his temperature was 101.2F and the physical examination was within normal limits except for rhinitis. Two hours after admission his temperature rose to 104.4F. The temperature rapidly fell and was normal 36 hours after admission. On the day following admission, examination revealed rales in the right lateral chest which cleared by the following day. At this time he was asymptomatic except for generalized malaise, anorexia, and a slightly productive cough. He was discharged on the fifth hospital day, asymptomatic except for cough. Chest x-rays were normal throughout his illness.

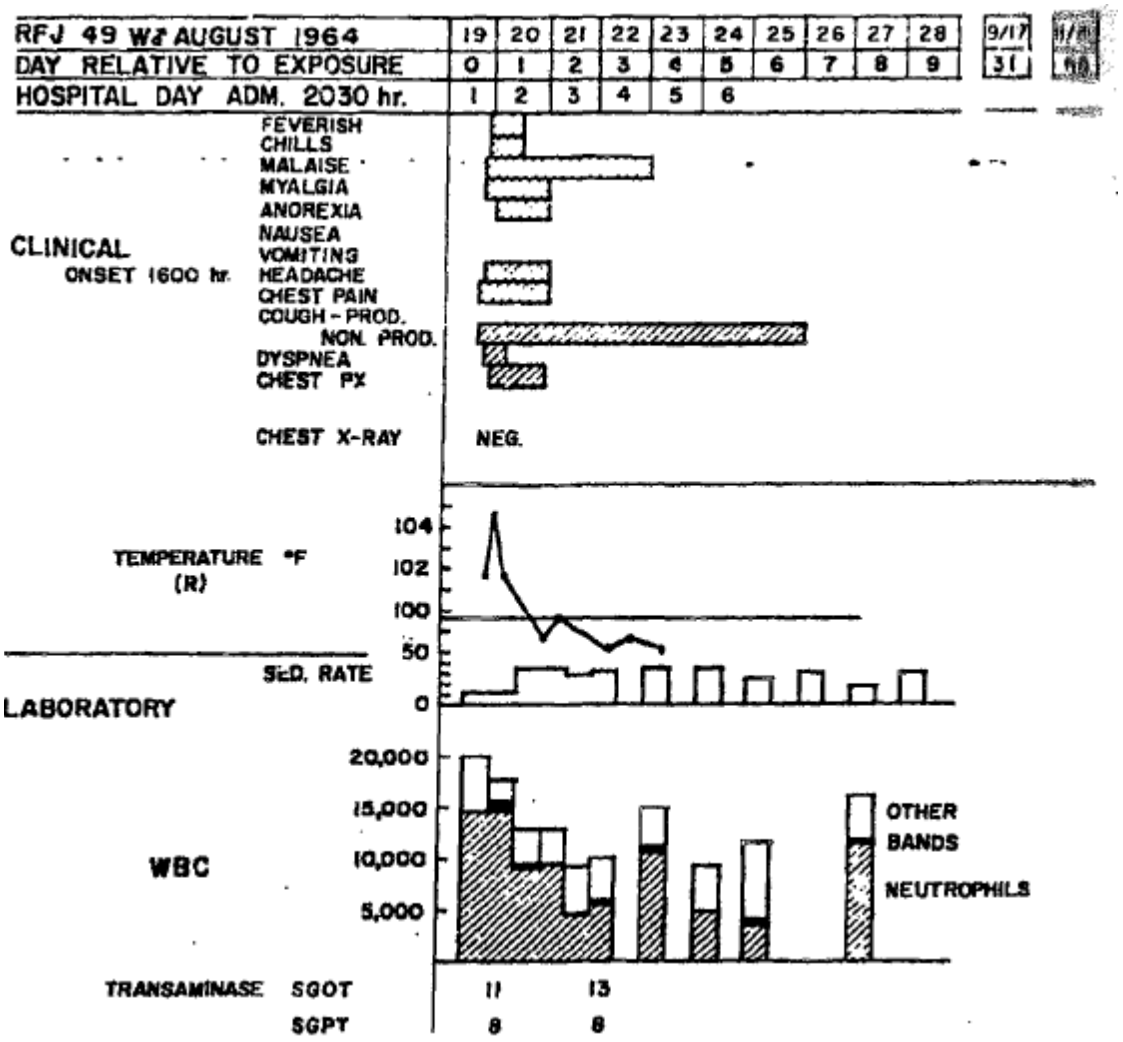

Figure A-4. Case Report 4, RFJ

Table A-4. Derived Latent Period and Duration of Symptoms, Case Report 4, RFJ

	Case #4 (RFJ)			
	Onset (Date/Time)	**Completion (Date/Time)**	**Latent Period* (hrs)**	**Duration (hrs)**
Hospitalization	8/19/64 20:30	8/24/64 12:00	11.5	111.5
Clinical Onset	8/19/64 16:00	(N/A)	7	
Feverish	8/19/64 20:30	8/20/64 12:00	11.5	15.5
Chills	8/19/64 20:30	8/20/64 12:00	11.5	15.5
Malaise	8/19/64 18:00	8/23/64 0:00	9	78
Myalgia	8/19/64 18:00	8/21/64 0:00	9	30
Anorexia	8/20/64 0:00	8/21/64 0:00	15	24
Nausea	(Not Reported)			
Vomiting	(Not Reported)			
Headache	8/19/64 18:00	8/21/64 0:00	9	30
Chest Pain	8/19/64 16:00	8/21/64 0:00	7	32
Cough - Productive	(Not Reported)			
Cough - Nonproductive	8/19/64 16:00	8/26/64 0:00	7	152
Dyspnea	8/19/64 18:00	8/20/64 6:00	9	12
Chest Px	8/19/64 20:30	8/21/64 0:00	11.5	27.5
Elevated Temp	8/19/64 20:30	8/21/64 12:00	11.5	39.5

*Relative to assumed exposure time of 09:00 hours on 8/19/64 (start of first presumed exposure period).

E.A.T. (Figure A-5) This 39-year-old Caucasian, male, animal caretaker was admitted at 2230 hours on the day of exposure. He had been well until 1630 hours when he developed a nonproductive cough, fever, chilliness, and frontal headache. On admission, his temperature was 103F. The physical examination was normal except for slight tachypnea while talking. His chest x-rays were normal. The temperature remained between 102–103F for the first 48 hours, and then fell gradually to normal by the fifth hospital day. The patient felt relatively well after the first night of hospitalization except of a headache, nonproductive cough, and anorexia, all of which had improved by the time of discharge on the sixth hospital day. After discharge he had a non productive cough for about two days and this gradually disappeared.

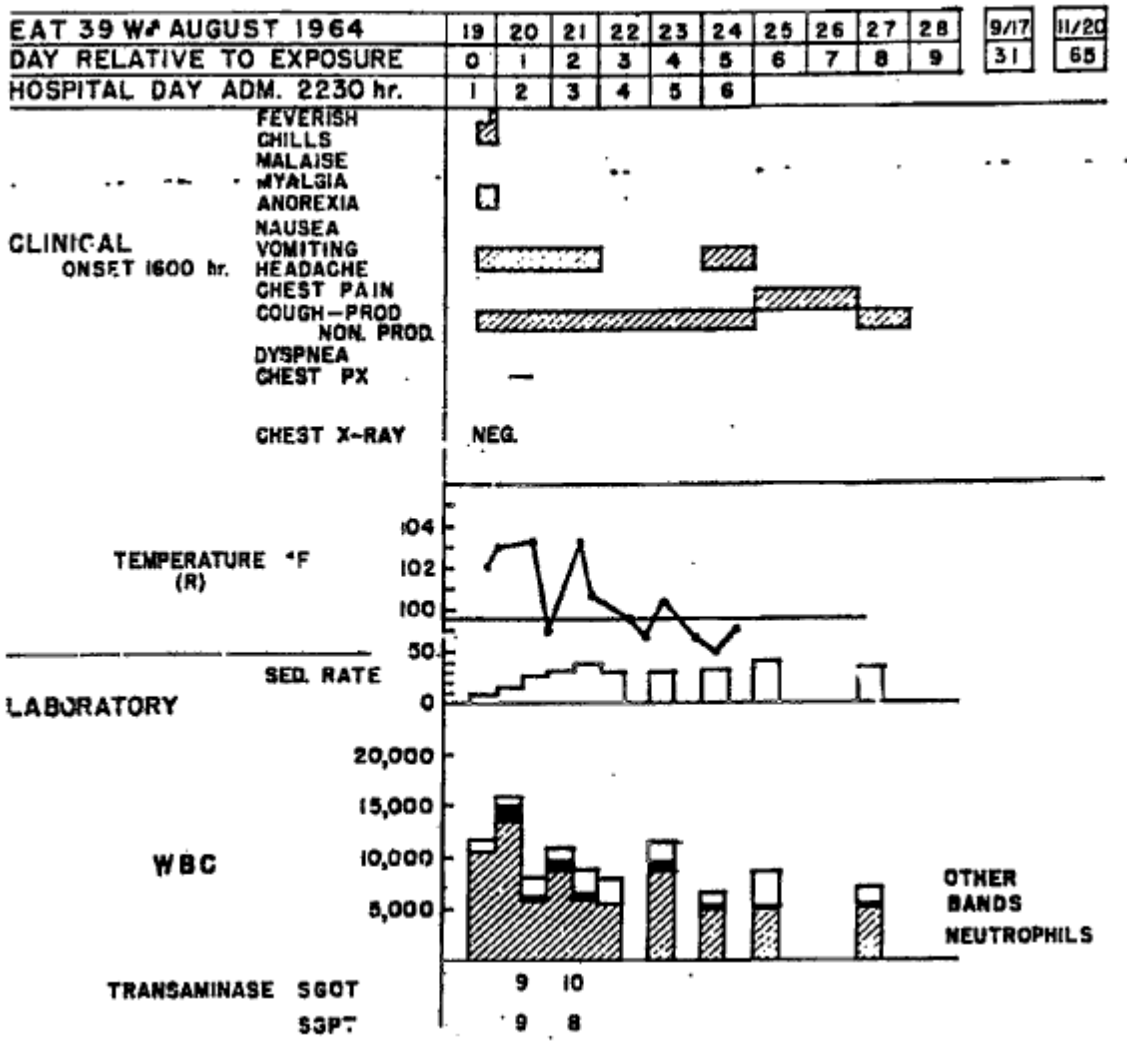

Figure A-5. Case Report 5, EAT

Table A-5. Derived Latent Period and Duration of Symptoms, Case Report 5, EAT

	Case #5 (EAT)			
	Onset (Date/Time)	**Completion (Date/Time)**	**Latent Period* (hrs)**	**Duration (hrs)**
Hospitalization	8/19/64 22:30	8/25/64 12:00	13.5	133.5
Clinical Onset	8/19/64 16:00	(N/A)	7	
Feverish	8/19/64 22:30	8/20/64 0:00	13.5	1.5
Chills	8/19/64 16:00	8/20/64 0:00	7	8
Malaise	(Not Reported)			
Myalgia	(Not Reported)			
Anorexia	8/19/64 16:00	8/20/64 0:00	7	8
Nausea	(Not Reported)			
Vomiting	(Not Reported)			
Headache	8/19/64 16:00	8/22/64 0:00	7	56
Chest Pain	(Not Reported)			
Cough - Productive	8/25/64 0:00	8/27/64 0:00	135	48
Cough - Nonproductive	8/19/64 16:00	8/28/64 0:00	7	200
Dyspnea	(Not Reported)			
Chest Px	(Not Reported)			
Elevated Temp	8/19/64 22:30	8/23/64 10:30	13.5	84

*Relative to assumed exposure time of 09:00 hours on 8/19/64 (start of first presumed exposure period).

A.C. (Figure A-6) This 37-year-old Caucasian, male, Sergeant was admitted at 2200 hours on the day of exposure. He had been well until about four hours prior to admission when he developed a slightly productive cough, headache, and fever. The patient was a heavy smoker and stated that he usually had a productive cough. He had no gastrointestinal symptoms, dyspnea, chest pain or myaigia. On admission, his temperature was 100.0F otherwise the physical examination was negative. His temperature rose to 101.8F within a few hours of admission and continued between 101 and 102F for the next 24 hours, then gradually fell to normal during the next two to three days. The patient developed some abdominal fullness and discomfort on the following admission but did not have other gastrointestinal symptoms. His cough became more productive of clear tenacious sputum but gradually improved over a seven day period. He was discharged on the sixth day, asymptomatic except for the nonproductive cough. The chest x-ray on admission showed an increase in peribronchial markings. Serial x-rays showed a decrease in the markings and a gradual return to normal.

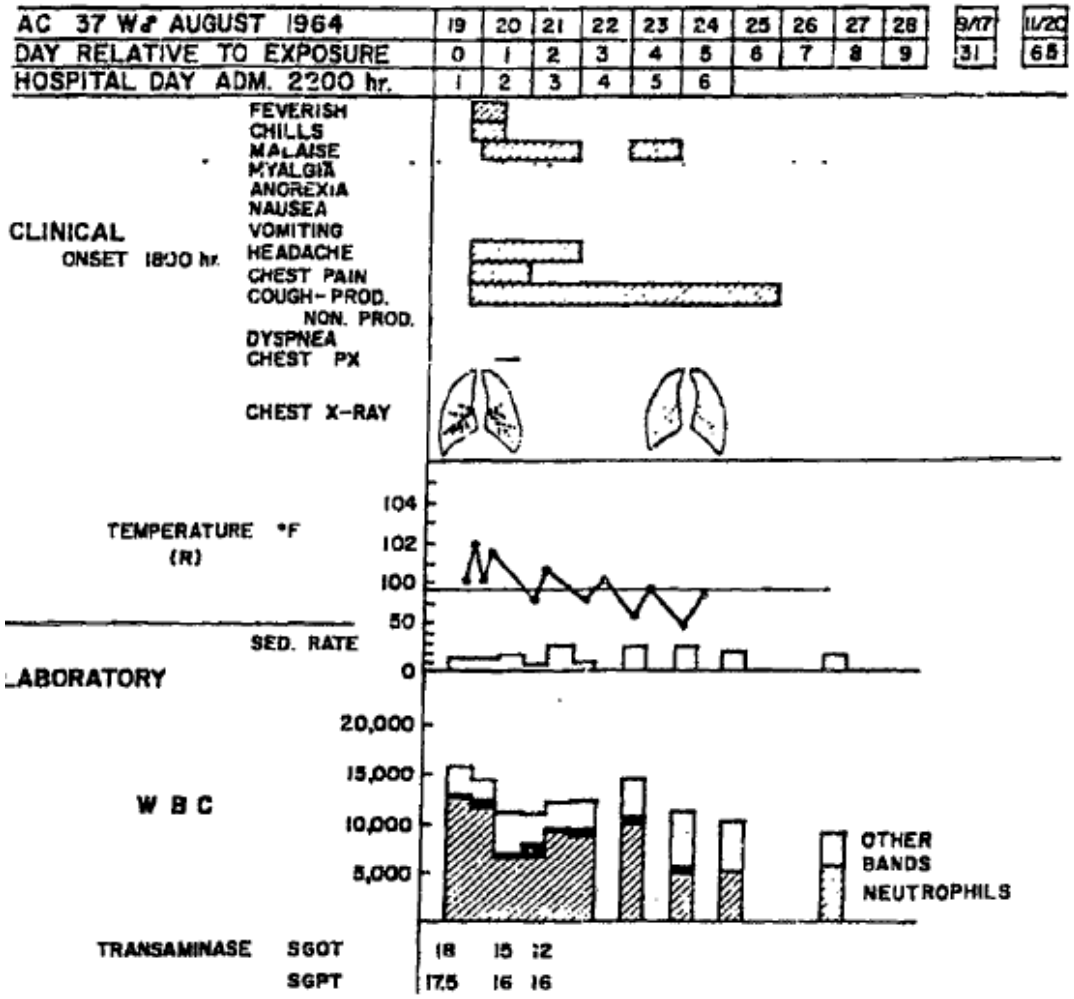

Figure A-6. Case Report 6, AC

Table A-6. Derived Latent Period and Duration of Symptoms, Case Report 6, AC

	Case #6 (AC)			
	Onset (Date/Time)	**Completion (Date/Time)**	**Latent Period* (hrs)**	**Duration (hrs)**
Hospitalization	8/19/64 22:00	8/25/64 12:00	13	134
Clinical Onset	8/19/64 18:00	(N/A)	9	
Feverish	8/19/64 18:00	8/20/64 12:00	9	18
Chills	8/19/64 18:00	8/20/64 12:00	9	18
Malaise	8/20/64 0:00	8/24/64 0:00	15	96
Myalgia	(Not Reported)			
Anorexia	(Not Reported)			
Nausea	(Not Reported)			
Vomiting	(Not Reported)			
Headache	8/19/64 18:00	8/22/64 0:00	9	54
Chest Pain	8/19/64 18:00	8/21/64 0:00	9	30
Cough - Productive	8/19/64 18:00	8/26/64 0:00	9	150
Cough - Nonproductive	(Not Reported)			
Dyspnea	(Not Reported)			
Chest Px	(Not Reported)			
Elevated Temp	8/19/64 22:00	8/23/64 0:00	13	74

*Relative to assumed exposure time of 09:00 hours on 8/19/64 (start of first presumed exposure period).

A.L.H. (Figure A-7) This 40-year-old Caucasian, Colonel, veterinarian was admitted at 0445 hours on the day following exposure. At 1800 hours on the day of exposure, he was afebrile but described an unusual sensation in his anterior chest as "Tightness." His temperature was normal and he was asymptomatic when he went to bed at 2300 hours. At 0400 hours the next morning he awoke because of cough and a febrile sensation. On admission, his temperature was 103F and the remainder of the physical examination was within normal limits. Several hours after admission his headache became more severe and he had cough on deep inspiration. The headache improved within 24 hours and the cough gradually improved over the next six days. He had no gastrointestinal manifestations until he ate breakfast on the morning of admission at which time he became nauseated. The anorexia and nausea continued only for a day or two and then his appetite improved. He was discharged on the fourth hospital day completely asymptomatic except for the cough. The chest x-ray on the morning of admission showed an area of discoid atelectasis in the left lower lobe. A film taken day three postexposure showed incomplete resolution of this area but an x-ray two weeks after exposure was completely normal.

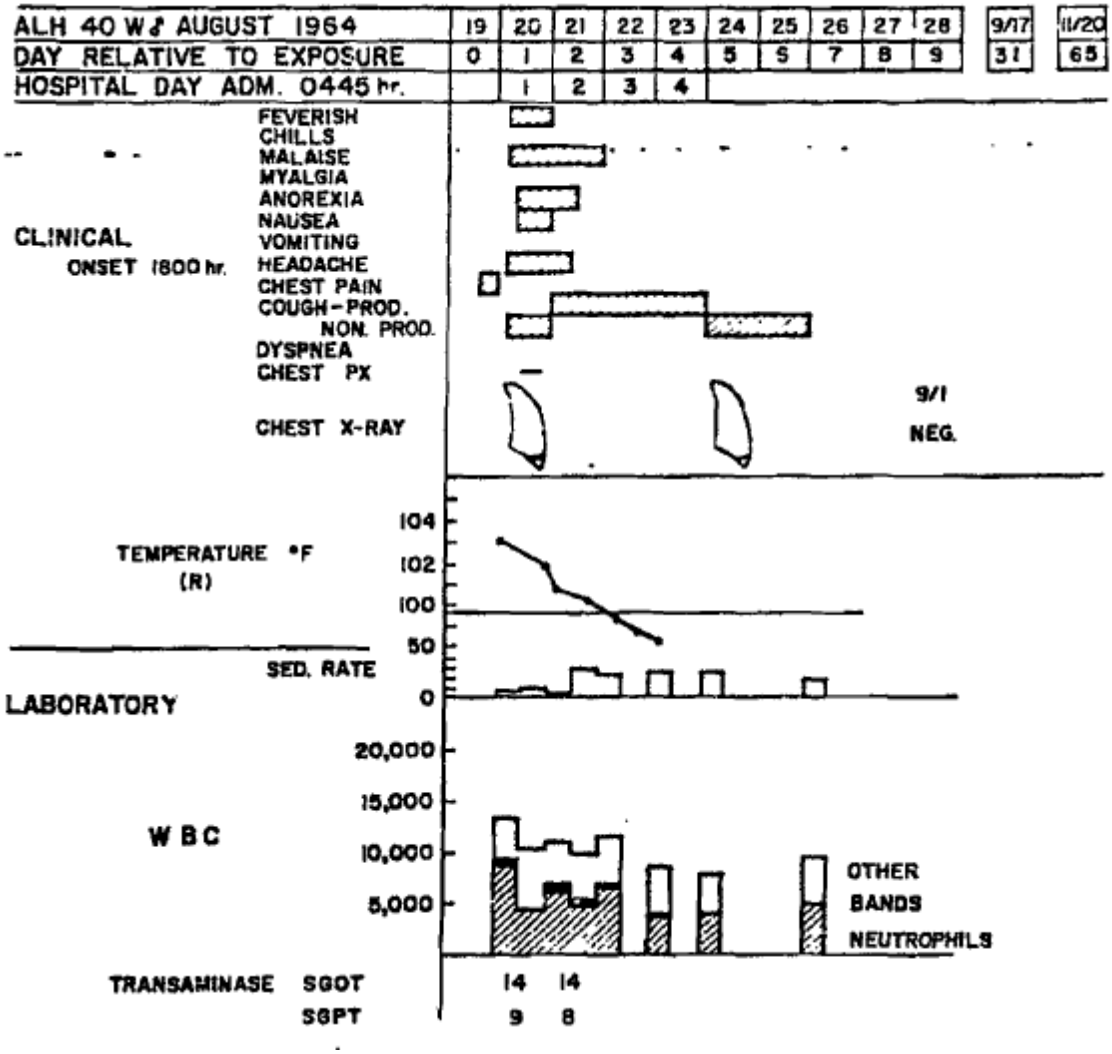

Figure A-7. Case Report 7, ALH

Table A-7. Derived Latent Period and Duration of Symptoms, Case Report 7, ALH

	Case #7 (ALH)			
	Onset (Date/Time)	**Completion (Date/Time)**	**Latent Period* (hrs)**	**Duration (hrs)**
Hospitalization	8/20/64 4:45	8/23/64 12:00	19.75	79.25
Clinical Onset	8/19/64 18:00	(N/A)	9	
Feverish	8/20/64 4:45	8/21/64 0:00	19.75	19.25
Chills	(Not Reported)			
Malaise	8/20/64 4:45	8/22/64 0:00	19.75	43.25
Myalgia	(Not Reported)			
Anorexia	8/20/64 8:45	8/21/64 12:00	23.75	27.25
Nausea	8/20/64 8:45	8/21/64 0:00	23.75	15.25
Vomiting	(Not Reported)			
Headache	8/20/64 4:45	8/21/64 12:00	19.75	31.25
Chest Pain	8/19/64 18:00	8/20/64 0:00	9	6
Cough - Productive	8/21/64 0:00	8/24/64 0:00	39	72
Cough - Nonproductive	8/20/64 4:45	8/26/64 0:00	19.75	139.25
Dyspnea	(Not Reported)			
Chest Px	(Not Reported)			
Elevated Temp	8/20/64 4:45	8/22/64 0:00	19.75	43.25

*Relative to assumed exposure time of 09:00 hours on 8/19/64 (start of first presumed exposure period).

R.W.K. (Figure A-8) This 32-year-old Caucasian, male, laboratory technician was admitted at 2230 hours on the day of exposure. The patient one of the two test unit operators, had felt well until about 1 hour prior to admission when he suddenly developed a nonproductive cough, retrosternal chest pain, headache, and a shaking chill. While being admitted to the hospital the patient became nauseated and vomited several times and had a second shaking chill. Temperature on admission was 101.8F. The physical examination was within normal limits except for a nonproductive cough. The chest x-ray was normal. His temperature ranged between 102 and 103F for about 48 hours and then gradually dropped to normal. On the day following admission he was found to have hepatomegaly. Anorexia, malaise, and tiredness continued during the patient's entire hospitalization. The chest pain, present on admission, improved within 24 hours, but on the third hospital day he developed shortness of breath and anterior chest pain, aggravated by deep breathing. Serial electrocardiograms were within normal limits. His urine revealed a trace of bile and he developed a rise in his SGOT and SGPT to 100 and 145 units respectively on the fifth day of hospitalization. The serum transaminases gradually came down to normal over the next five days. Other liver tests revealed an elevated BSP and alkaline phosphatase. The chest pain gradually improved over a 24 hr period and the liver was not palpable after the fourth hospital day. The etiology of the chest pain was unknown but our clinical impression was that it did not represent pericarditis or myocarditis. The liver abnormalities were believed due to a non-specific acute toxic hepatitis. All symptoms and laboratory findings had improved by the time of discharge which was the seventh hospital day.

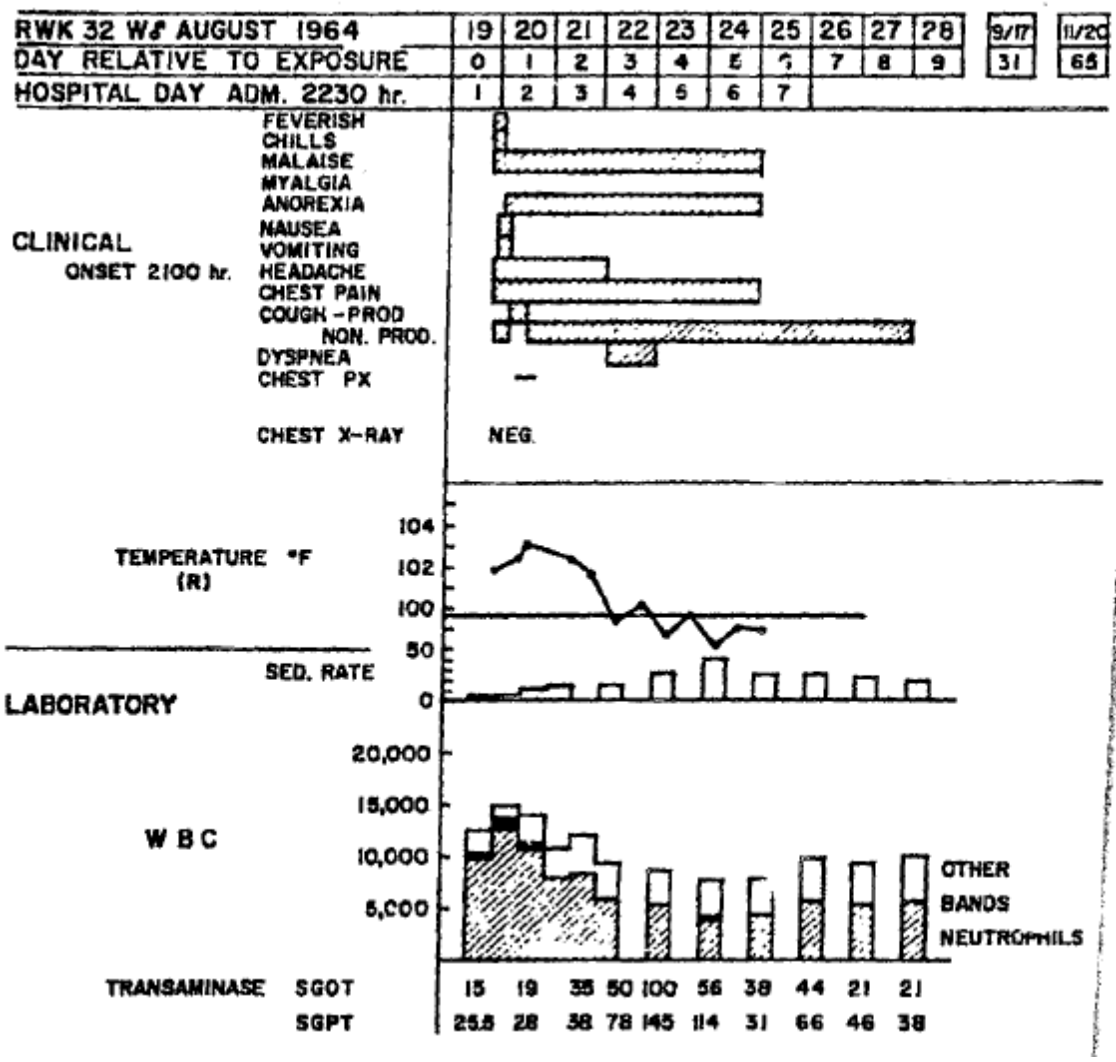

Figure A-8. Case Report 8, RWK

Table A-8. Derived Latent Period and Duration of Symptoms, Case Report 8, RWK

	Case #8 (RWK)			
	Onset (Date/Time)	**Completion (Date/Time)**	**Latent Period* (hrs)**	**Duration (hrs)**
Hospitalization	8/19/64 22:30	8/26/64 12:00	13.5	157.5
Clinical Onset	8/19/64 21:00	(N/A)	12	
Feverish	8/19/64 21:00	8/20/64 2:30	12	5.5
Chills	8/19/64 21:00	8/20/64 2:30	12	5.5
Malaise	8/19/64 21:00	8/25/64 0:00	12	123
Myalgia	(Not Reported)			
Anorexia	8/20/64 2:30	8/25/64 0:00	17.5	117.5
Nausea	8/19/64 22:30	8/20/64 6:30	13.5	8
Vomiting	8/19/64 22:30	8/20/64 6:30	13.5	8
Headache	8/19/64 21:00	8/22/64 0:00	12	51
Chest Pain	8/19/64 21:00	8/25/64 0:00	12	123
Cough - Productive	8/20/64 6:30	8/20/64 12:00	21.5	5.5
Cough - Nonproductive	8/19/64 21:00	8/28/64 0:00	12	195
Dyspnea	8/22/64 0:00	8/23/64 0:00	63	24
Chest Px	(Not Reported)			
Elevated Temp	8/19/64 22:30	8/23/64 0:00	13.5	73.5

*Relative to assumed exposure time of 09:00 hours on 8/19/64 (start of first presumed exposure period).

J.F.F. (Figure A-9) This 30-year-old Caucasian, Captain, veterinarian was admitted at 2200 hours on the day of exposure. He was well until about 1 hour prior to admission when he suddenly developed generalized chest pain and headache. He had a mild nonproductive cough but no other pulmonary symptoms. On admission, his temperature was 102.4F. The physical examination was within normal limits except for hyperactive bowel sounds. His chest x-ray was normal. The temperature remained between 102 and 103F for the first 36 hours after admission and then rapidly fell to normal. On the morning following admission the patient developed nausea and vomiting. Anorexia was present until the fifth hospital day, at which time he was discharged asymptomatic. In contrast to previous cases, this patient did not manifest leukocytosis.

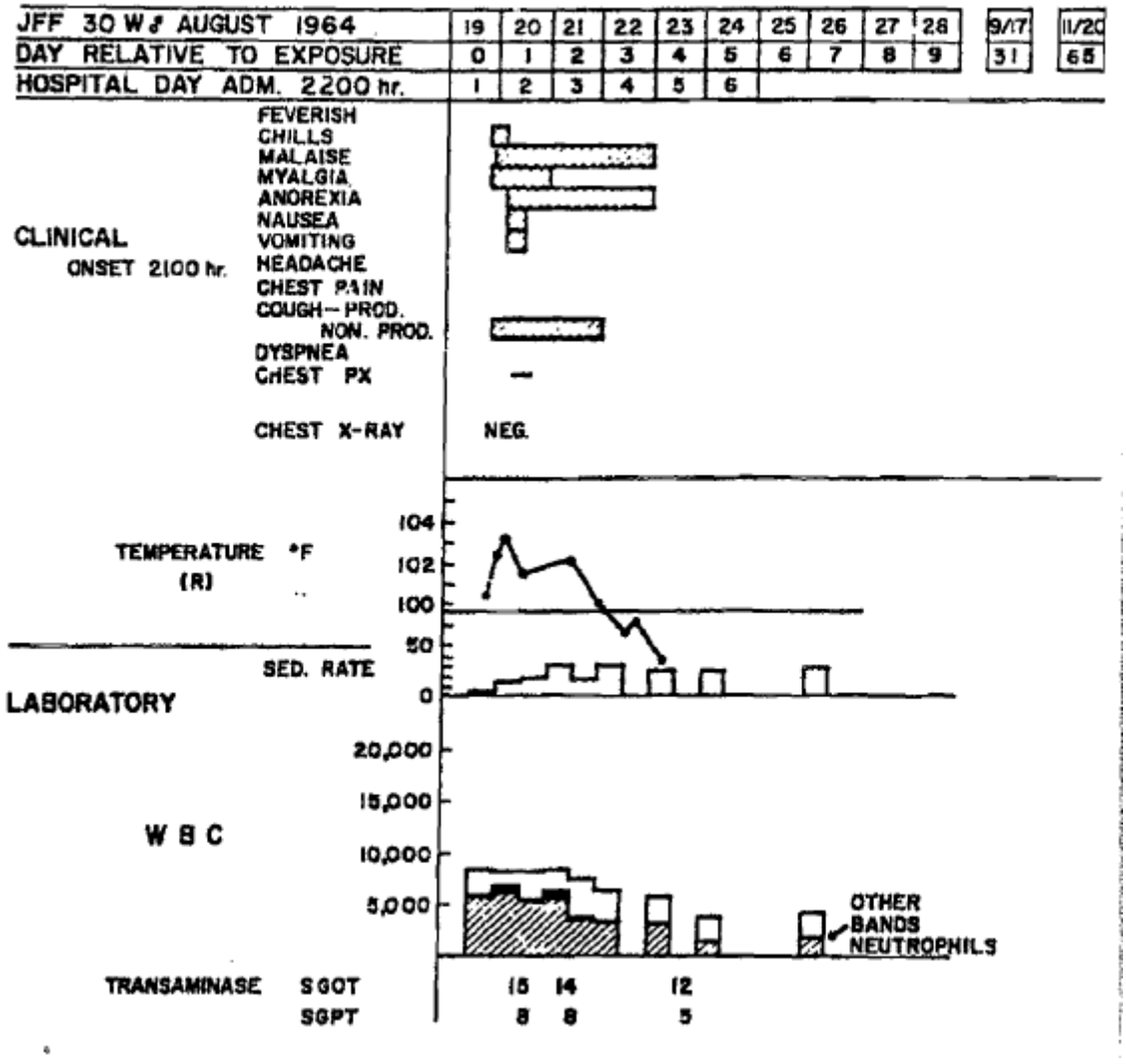

Figure A-9. Case Report 9, JFF

Table A-9. Derived Latent Period and Duration of Symptoms, Case Report 9, JFF

	Case #9 (JFF)			
	Onset (Date/Time)	**Completion (Date/Time)**	**Latent Period* (hrs)**	**Duration (hrs)**
Hospitalization	8/19/64 22:00	8/24/64 12:00	13	110
Clinical Onset	8/19/64 21:00	(N/A)	12	
Feverish	(Not Reported)			
Chills	8/19/64 21:00	8/20/64 4:00	12	7
Malaise	8/19/64 22:00	8/23/64 0:00	13	74
Myalgia	8/19/64 21:00	8/21/64 0:00	12	27
Anorexia	8/20/64 4:00	8/23/64 0:00	19	68
Nausea	8/20/64 4:00	8/20/64 12:00	19	8
Vomiting	8/20/64 4:00	8/20/64 12:00	19	8
Headache	(Not Reported)			
Chest Pain	(Not Reported)			
Cough - Productive	(Not Reported)			
Cough - Nonproductive	8/19/64 21:00	8/22/64 0:00	12	51
Dyspnea	(Not Reported)			
Chest Px	(Not Reported)			
Elevated Temp	8/19/64 22:00	8/22/64 0:00	13	50

*****Relative to assumed exposure time of 09:00 hours on 8/19/64 (start of first presumed exposure period).

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Appendix B
Illustrations

Figures

Tables

Approved for public release; distribution is unlimited.

Appendix C
References

Chapter 1 - Introduction

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Appendix D
Abbreviations

AMA	American Medical Association
AMedP-8(C)	Allied Medical Publication 8(C): NATO Planning Guide for the Estimation of CBRN Casualties
CBRN	Chemical, Biological, Radiological, and Nuclear
CDF	Cumulative Distribution Function
CFU	Colony Forming Unit
DSWA	Defense Special Weapons Agency
DTRA	Defense Threat Reduction Agency
GPIPD	Guinea Pig Interperitoneal Dose
ID	Infective Dose
JAMA	Journal of the American Medical Association
LD	Lethal Dose
MRID	Median Man Respiratory Infective Dose
MRLD	Median Man Respiratory Lethal Dose
MRV	Military Research Volunteers
NATO	North Atlantic Treaty Organization
NBC	Nuclear, Chemical and Biological
OTSG	U.S. Army Office of The Surgeon General
PCR	Polymerase Chain Reaction
PSR	Pacific Sierra Research Corporation
RIVFID	Rhesus Intravenous Fever Illness Dose
RIVEID	Rhesus Intravenous Emesis-Diarrhea Illness Dose
RIVID	Rhesus Intravenous Effective/Infective Dose
RIVLD	Rhesus Median Intravenous Lethal Dose
RREDID	Rhesus Respiratory Emesis-Diarrhea Illness Dose
RRFID	Rhesus Respiratory Fever Illness Dose
RRLD	Rhesus Respiratory Lethal Dose
SEA	Staphylococcal Enterotoxin A

SEB	Staphylococcal Enterotoxin B
SME	Subject Matter Expert
TSS	Toxic Shock Syndrome
USAMRIID	United States Army Medical Research Institute for Infectious Disease
VEE	Venezuelan Equine Encephalitis

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14. ABSTRACT

The U.S. Army Office of The Surgeon General (OTSG) tasked IDA with developing human response models for five prospective non-contagious biological warfare agents, using the methodology contained in *Allied Medical Publication 8(C): NATO Planning Guide for the Estimation of CBRN Casualties (AMedP-8(C))*. The five agents considered in this document are brucellosis, glanders, Q fever, staphylococcal enterotoxin B (SEB), and tularemia. For each agent, the authors propose parameters and values for models of infectivity, lethality, incubation period, and duration of illness. The authors also describe profiles of illness over time for each agent based on symptoms and their associated severity, using the scale developed in AMedP-8(C). The work described in this document is based on an extensive review of available literature and subsequent evaluation of existing models, experimental data sets—both human and animal—and clinical case studies.

15. SUBJECT TERMS

Casualty estimation, biological warfare agents, CBRN, modeling, AMedP-8, brucellosis, glanders, Q fever, staphylococcal enterotoxin B, SEB, tularemia

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