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TECHNICAL REPORT

Burkholderia pseudomallei Data Gap Analysis

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14. ABSTRACT

The purpose of this review is to identify the major biodefense-relevant data gaps critical to better understanding Burkholderia pseudomallei infections (melioidosis)and how they are acquired, diagnosed, treated and prevented. The following data areas are addressed: epidemiology, animal models, microbiology and genomics, vaccine and medical countermeasures, and predictive modeling.

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CONVERSION TABLE

Conversion Factors for U.S. Customary to metric (SI) units of measurement.

MULTIPLY →	BY →	TO GET
TO GET ←	BY ←	DIVIDE
angstrom	1.000 000 x E -10	meters (m)
atmosphere (normal)	1.013 25 x E +2	kilo pascal (kPa)
bar	1.000 000 x E +2	kilo pascal (kPa)
barn	1.000 000 x E -28	meter^2 (m^2)
British thermal unit (thermochemical)	1.054 350 x E +3	joule (J)
calorie (thermochemical)	4.184 000	joule (J)
cal (thermochemical/cm^2)	4.184 000 x E -2	mega joule/m^2 (MJ/m^2)
curie	3.700 000 x E +1	*giga bacquerel (GBq)
degree (angle)	1.745 329 x E -2	radian (rad)
degree Fahrenheit	$t_k = (t^of + 459.67)/1.8$	degree kelvin (K)
electron volt	1.602 19 x E -19	joule (J)
erg	1.000 000 x E -7	joule (J)
erg/second	1.000 000 x E -7	watt (W)
foot	3.048 000 x E -1	meter (m)
foot-pound-force	1.355 818	joule (J)
gallon (U.S. liquid)	3.785 412 x E -3	meter^3 (m^3)
inch	2.540 000 x E -2	meter (m)
jerk	1.000 000 x E +9	joule (J)
joule/kilogram (J/kg) radiation dose absorbed	1.000 000	Gray (Gy)
kilotons	4.183	terajoules
kip (1000 lbf)	4.448 222 x E +3	newton (N)
kip/$inch^2$ (ksi)	6.894 757 x E +3	kilo pascal (kPa)
ktap	1.000 000 x E +2	newton-second/m^2 ($N-s/m^2$)
micron	1.000 000 x E -6	meter (m)
mil	2.540 000 x E -5	meter (m)
mile (international)	1.609 344 x E +3	meter (m)
ounce	2.834 952 x E -2	kilogram (kg)
pound-force (lbs avoirdupois)	4.448 222	newton (N)
pound-force inch	1.129 848 x E -1	newton-meter (N-m)
pound-force/inch	1.751 268 x E +2	newton/meter (N/m)
pound-force/$foot^2$	4.788 026 x E -2	kilo pascal (kPa)
pound-force/$inch^2$ (psi)	6.894 757	kilo pascal (kPa)
pound-mass (lbm avoirdupois)	4.535 924 x E -1	kilogram (kg)
pound-mass-$foot^2$ (moment of inertia)	4.214 011 x E -2	kilogram-meter^2 ($kg-m^2$)
pound-mass/$foot^3$	1.601 846 x E +1	kilogram-meter^3 (kg/m^3)
rad (radiation dose absorbed)	1.000 000 x E -2	**Gray (Gy)
roentgen	2.579 760 x E -4	coulomb/kilogram (C/kg)
shake	1.000 000 x E -8	second (s)
slug	1.459 390 x E +1	kilogram (kg)
torr (mm Hg, 0^0 C)	1.333 22 x E -1	kilo pascal (kPa)

*The bacquerel (Bq) is the SI unit of radioactivity; 1 Bq = 1 event/s.

**The Gray (GY) is the SI unit of absorbed radiation.

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PREFACE

The research work described in this report was conducted for the Defense Threat Reduction Agency (DTRA) under contract number DTRA01-03-D-0014-0030. The request for this brief study was made by Dr. Chris Kiley of DTRA's Information Systems Capability Development Office (J9CBI) with the concurrence of Mr. Rick Fry of the same office, the Contract Officer's Representative for this contract. The authors would like to thank Mr. Fry for his leadership and management of the Health and Human Effects Modeling for CBRN program.

1.0 INTRODUCTION

Often mistaken for glanders, melioidosis was recognized as a distinct disease in 1911 when the then unknown bacterium *Burkholderia pseudomallei* was clinically isolated by Alfred Whitmore in Burma (Myanmar). Figure 1-1 illustrates the prevalence of melioidosis worldwide. Since the addition of *B. pseudomallei* to the list of Category B Agents by the Centers for Disease Control and Prevention (CDC) in 2001, its profile has been raised from that of a disease endemic primarily to southeast Asia and northern Australia to one of global significance. The concern over the organism's potential as a biological weapon has resulted in an increase in international defense related research activities. With that in mind, the purpose for conducting this review is to identify the major biodefense relevant data gaps critical to better understanding *B. pseudomallei* infections and how they are acquired, diagnosed, treated and possibly prevented.

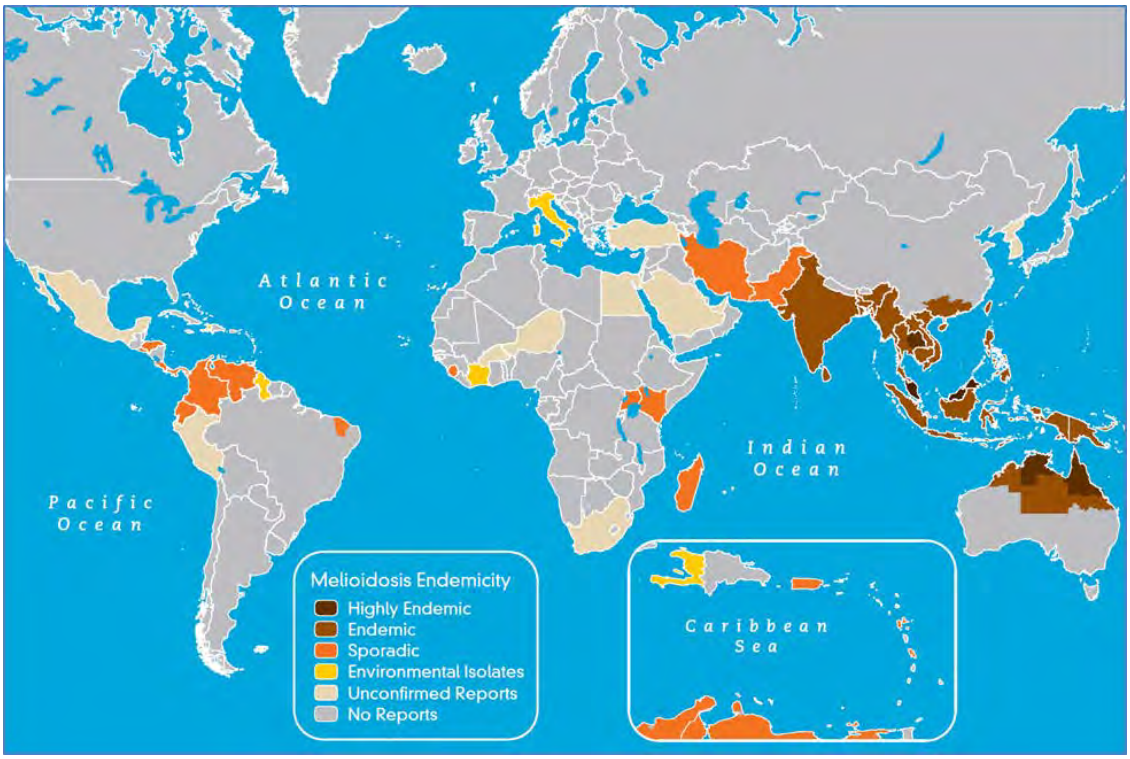

Figure 1-1. Worldwide melioidosis endemicity (courtesy of CDC).

2.0 EPIDEMIOLOGY

Since its discovery, *B. pseudomallei* has become recognized as a significant public health threat in the tropical regions of the globe where it is considered endemic, living in the soil and water. As a result there has been significant effort invested into characterizing melioidosis from a public health perspective. Epidemiologically there are many publications on clinically identified populations – some spanning several decades and thousands of patients (Table 2-1). Much of the data has excellent demographic and clinical resolution including age, sex, symptoms, duration of illness, risk factors, treatment and outcome. Community acquired presentation varies and is not always correlated to the modes of infection - primarily cutaneous, inhalation and enteral. Presentations include pneumonia, genitourinary, cutaneous, general bacteremia, septic arthritis and neurological melioidosis. Given the volume of epidemiological data collected it is unlikely that there would be significant gaps; however, a more detailed analysis is warranted. One fact worth noting is that melioidosis commonly infects people with depressed immune systems, including those who are chronic alcoholics, kava users (Australia), chronic drug users, or diabetic. However, HIV does not seem to be a factor.

Table 2-1. Published melioidosis epidemiology studies by infection type.

Infection Type	Study Year(s)	Location	Patients	Reference
Pulmonary	2011	Sri Lanka	1	Perera, 2012
Pulmonary	2007-2010	Cambodia	39	Rammaert, 2011
Various	1985-2009	Darwin Australia	540	Currie, 2010
Various	1997-2006	Northeast Thailand	2243	Limmathurotsakul, 2011
Various	2005-2008	Malaysia	145	Hassan, 2010
Pulmonary Sepsis	2007	Malaysia	1	Kandasamy, 2007
Recurrent	1986-2004	Northeast Thailand	889	Limmathurotsakul, 2006
Various	1947-2005	Global Travelers	30	Inglis, 2006
Various	2000-2003	Pahang, Malaysia	139	How, 2005
Various	1989-2003	Northern Australia	364	Currie, 2004
Various	2001-2002	Northern Australia	47	Cheng, 2003
Pulmonary	1966	United States Military Personnel	9	Spotnitz, 1967
Pulmonary	1989-1999	Northern Australia	252	Currie, 2000

A sub-population of melioidosis patients who are successfully treated continues to carry the bacteria latently and eventually experience recurrent symptoms – sometimes decades later. This

phenomenon is not well understood beyond the population statistics. Research into quorum sensing may reveal clues into how *B. pseudomallei* can remain latent for extended periods of time without causing illness in humans. [Ulrich, 2004]

Infections resulting from the inhalation of aerosolized *B. pseudomallei* are not uncommon in endemic regions. As Figure 2-1 illustrates, increased incidence of respiratory infections has been correlated to increased rainfall in Australia. The researchers suspect heavy monsoon rains combined with high winds are responsible for seasonal shifts toward inhalation infections, [Currie, 2003]. This would allow for many of the case studies from Table 1 to correlate to aerosolized attacks with *B. pseudomallei* , especially if a dose reconstruction can be derived from the data.

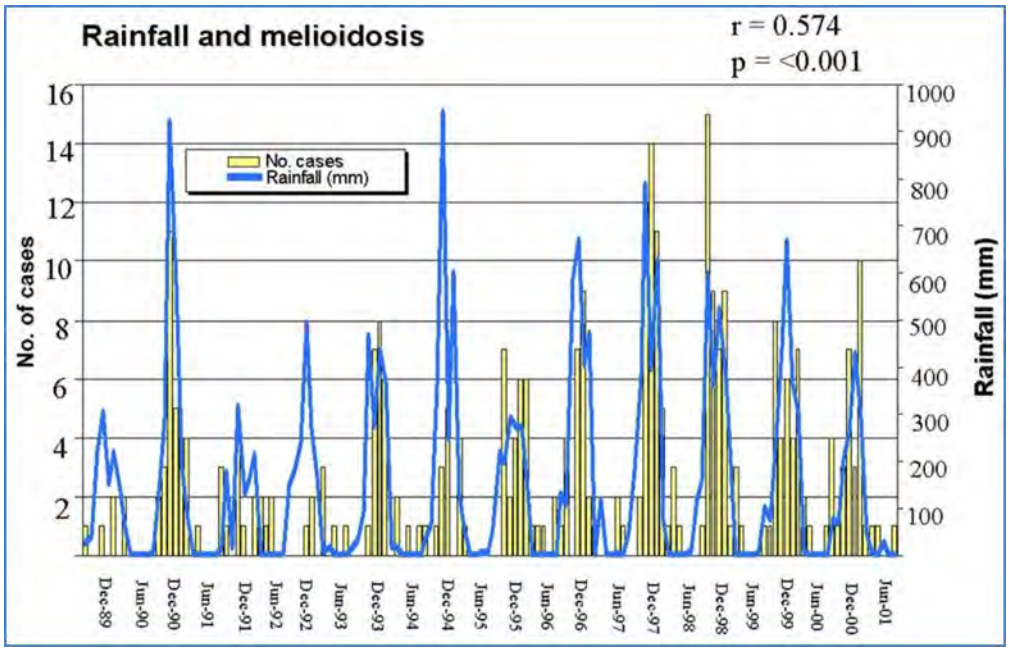

Figure 2-1. Monthly rainfall and melioidosis cases during a 12 year study period, Australia [Currie, 2003].

3.0 LABORATORY RESEARCH

The following subsections review laboratory studies involving animal models, genomics, and vaccines/medical countermeasures.

3.1 ANIMAL MODELS

A variety of animal models have been utilized in melioidosis research to assess aspects of infection, illness progression, treatment, and probability of survival. Animals used in this research include mice, hamsters, rats, ferrets, guinea pigs, rabbits, pigs, and non-human primates. By far the most widely used is the mouse model and the most common mice used are the BALB/c and B57BL/6 [Patel, 2011].

Mouse models have been utilized to study the entire spectrum of exposures including intravenous, intraperitoneal, subcutaneous, intranasal, aerosol, intranasal/oral and chronic. To a certain degree mice are ideal surrogates for studying melioidosis since they exhibit similar levels of susceptibility to infection, proinflammatory response and involvement of target organs [Warawa, 2010]. A caveat to this is that some mouse strains have demonstrated orders of magnitude variations in dose response values [Froude, 2011; Patel, 2011; Warawa, 2010]. There have been at least ten publications using aerosolized *B. pseudomallei* and an additional 17 using intranasal inoculations in mice [Warawa, 2010]. The models have produced LD_{50} and ID_{50} numbers ranging from 5 to $1.47x10^3$ colony forming units. Also, when mice are inoculated intranasally there seems to be a higher incidence of meningitis than is seen in the human data [Warawa, 2010]. This is likely due, in part, to the structural and tissue differences between the mouse and human respiratory tracts.

Syrian Hamsters are commonly used as a model animal for vaccine development due to their high susceptibility to *B. pseudomallei* infection. Diabetic rats are also common since they are acutely susceptible to *B. pseudomallei* and often die within 48hrs [Patel, 2011].

Non-human primate (NHP) models are not well represented in the published data. There are two references to actual studies involving rhesus mecaques (subcutaneous inoculation) and Hamadryas baboons (intraparetoneal and subcutaneous inoculations) [Warawa, 2010]. With the

afore mentioned interest in weaponized forms of melioidosis there has been some anecdotal reference to developing new non-human primate models but thus far no publications have been identified [Warawa, 2010]. Another publication mentions the value of NHPs in vaccine development but also acknowledges the absence of mature models [Patel, 2011].

Despite the diversity of animal models used to study melioidosis the focus has been primarily on community acquired infections using a broad range of clinical isolates in non-standardized animal models making the results difficult to compare from one study to another. The absence of standardized mouse and non-human primate models coupled with well characterized if not standardized strains of *B. pseudomallei* make data correlation difficult [Warawa, 2010]. The use of larger numbers of animals in experiments would add confidence to the statistics as well [Tamarakar, 2008].

3.2 GENOMIC RESEARCH

Unlike anthrax or small pox, *B. pseudomallei* has never been weaponized and therefore lacks specific strains on which to base animal model development or vaccine research. In 2004 the complete genomic sequences of *B. pseudomallei* (strain K96243) and *Burkholderia mallei* were published [Holden, 2004]. Since then research has progressed identifying key differences between *B. pseudomallei* and *B. mallei* [Godoy, 2003]. Today there are hundreds of clinically isolated *B. pseudomallei* strains collected and analyzed yet there doesn't appear to be a clear understanding as to how virulence varies or if any particular strains are more virulent than others. The development of new animal models and vaccines would benefit from having a clearer understanding of the variations inherent to *B. pseudomallei* strains.

3.3 VACCINE RESEARCH AND MEDICAL COUNTERMEASURES

There are no approved vaccines for melioidosis, however there are significant efforts focused on elucidating the *B. pseudomallei* virulence mechanisms, identifying vaccine targets and testing them in vitro and in vivo for efficacy. There are several types of vaccine candidates identified from literature including live attenuated, inactivated whole cell, sub-unit, and naked-DNA/dentritic cell vaccines [Peacock, 2012].

Live attenuated vaccines: all of the candidates were tested using mouse models however the *B. pseudomallei* strains used, dose and routes of exposure varied widely.

Inactivated whole cell vaccines: there are a variety of advantages (presents a wide range of antigens, easy to manufacture) and disadvantages (safety concerns and side effects) with such vaccines. There have been some studies using *Burkholderia thailandensis*.

Sub-unit vaccines: have the advantage of being highly specific and safe to administer. There is a large body of research on the use of such vaccines against intraperitoneal *B. pseudomallei* in mice with some specific virulence factors identified as targets. There is little evidence of this being effective against inhaled *B. pseudomallei* There is also the problem of genetic variability of *B. pseudomallei* potentially making a vaccine ineffective against certain strains.

Naked-DNA/dendritic cell vaccines: there are two publications reporting efficacy using a DNA vaccine against a *B. pseudomallei* flagellar subunit gene. However, the history for these types of vaccines has shown better efficacy in mouse models that in human trials. In addition to the naked-DNA vaccine approach dendritic cell vaccines are a relatively new approach that has yet to be proven using *B. pseudomallei* .

In the absence of an effective and approved vaccine there is no protective countermeasure against *B. pseudomallei* . Prophylaxis using antibiotics has been investigated in mice however there is no data confirming its efficacy in humans [Estes, 2010]

4.0 PREDICTIVE MODELS

A human effects model for exposure to *B. mallei* has been developed for Allied Medical Publication 8 (B) and the NBC Casualty and Resource Estimation Support Tool, however there is not a similar model for *B. pseudomallei* exposure. Its endemic nature and the natural human susceptibility (much greater than *B. mallei*) to *B. pseudomallei* make it a threat as a biological weapon and thus a candidate for developing a predictive model for human exposure. There are some key areas that would benefit from additional data including more consistent animal data using standardized animal models (including non-human primates), exposure methods (including aerosolized agent) and bacterial strains (with defined virulence potential). One publication was found which describes a dose response model for *B. pseudomallei* in mice. They cited the variability of the mouse data as a key problem with developing a valid model [Tamrakar, 2008].

5.0 CONCLUSIONS

For melioidosis and its causative agent *B. pseudomallei* there are an abundance of epidemiologic and demographic data however in others there is a distinct absence of human dose response and vaccination/prophylaxis data. There is also a lack of reliable aerosolized exposure data from animal experiments. A summary of the key points are listed below:

1. **Epidemiological Gaps**
    a. Gap 1 – no human dose response data; Impact – forced reliance upon animal models to correlate human dose response
2. **Animal Model Gaps**
    a. Gap 2 - little standardization of animal models; Impact – un-controlled variability in experimental results making dose response and vaccine efficacy, for example, difficult to quantify.
    b. Gap 3 – absence of a standardized non-human primate model ; Impact – although efforts may be under way to develop a NHP model without it the best potential human surrogates are not being utilized.
3. **Microbiology and Genomics Gaps**
    a. Gap 4 – no standardization of *B. pseudomallei* strains for conducting biodefense research; Impact – continued un-controlled variability in animal exposure data
    b. Gap 5 – poor understanding of the mechanisms involved in recurrent melioidosis; Impact – there will be a significant population or previously infected people who will relapse despite receiving necessary medical care
4. **Vaccine and Medical Countermeasure Gaps**
    a. Gap 6 – no approved vaccine for melioidosis; Impact – inability to reliably prevent infections
5. **Predictive Modeling Gaps**
    a. Gap 7 – no predictive planning tool available for consequence assessment; Impact - DoD may be incapable of mounting an adequate response to the release of weaponized *B. pseudomallei*

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DEFINITIONS, ACRONYMS, AND ABBREVIATIONS

ARA	Applied Research Associates, Inc.
BALB/c	Designation for a specific laboratory mouse strain
B57BL/6	Inbred mouse strain
B. mallei	*Burkholderia mallei*
B. pseudomallei	*Burkholderia pseudomallei*
CDC	Centers for Disease Control and Prevention
DNA	Deoxyribonucleic Acid
DTRA	Defense Threat Reduction Agency
HIV	Human immunodeficiency virus
ID_{50}	Infectious dose, 50%
LD_{50}	Lethal dose, 50%
NBC	Nuclear, Biological, and Chemical
NHP	Nonhuman primate

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