J Med CBR Def | Volume 8, 2010
Submitted 30 May 2010| Accepted 2 September 2010 | Revised 9 September 2010 | Published 17 September 2010

Tularemia: A Case Study In Medical Surveillance And Bioterrorism Preparedness

Joseph P. Dudley, M.S., Ph.D.

Science Applications International Corporation
12530 Parklawn Drive, Suite 350 Rockville MD 20852
Joseph.P.Dudley@saic.com

Suggested citation: Dudley, J P (2010), "Tularemia: A Case Study In Medical Surveillance And Bioterrorism Preparedness", JMedCBR 8, 17 September 2010, http://www.jmedcbr.org/issue_0801/Dudley/Dudley_09_10.html.

ABSTRACT

A incident that occurred in the Washington DC area during the summer of 2006 highlights the critical need for training primary care medical providers in the recognition and treatment of emerging diseases and biological agents of known importance. A patient presenting to the primary care facility of a major hospital facility in the Washington DC area with a history of recent exposure in an area with an ongoing tularemia outbreak with 10 of 13 principal symptoms of tularemia was unable to get tested for a possible tularemia infection, and was instructed to "… wait for the symptoms to become more severe" before reporting to the hospital Emergency Department for further evaluation and possible treatment. This incident highlights the continued limited success of efforts to ensure that civilian and military health care personnel in one of the highest bioterrorism risk areas of the United States, are both able and willing to recognize potentially anomalous or clinical symptoms and exposure patterns that could point to unwitting exposure to potential bioweapon pathogens, biological toxins, toxic chemicals, or radiological agents.

INTRODUCTION

The early detection and control of biological or chemical terrorist attacks or public health emergencies is dependent on the existence of strong and flexible public health system preparedness and response capabilities at the local, state, and national levels. Nursing professionals, emergency care responders, and physicians can perform a crucial role in our first-line defense against terrorism by detecting and reporting unusual or anomalous illness that may be indicative of possible accidental or occupational exposures to biological and chemical weapons agents. Primary health care providers and first responders should be considered especially important in this regard because it is they who will likely have first contact with exposed victims and thus will have the first opportunity to observe and report any unusual or apparently anomalous illnesses or injuries. The same is true of more prosaic but nonetheless real threats associated with outbreaks of more common infectious diseases, as well as the growing concerns

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associated with newly emerging and re-emerging zoonotic disease pathogens, and antibiotic-resistant strains of more common and widely distributed infectious disease pathogens.

Definition and Classification

Tularemia of particular importance and has been recognized as a widely distributed infectious disease.

The pathogen that causes Tularemia, *Francisella tularensis*, is a Class A biological weapons agent [Dennis, et al., 2001], occurs naturally across most of the continental US [Hayes, et al., 2002], and has a history of an exceptionally high frequency of accidental infections associated with laboratory exposures [Sulkin and Pike, 1951; Pike et al., 1965; Burke, 1977; Shapiro and Schwartz, 2002; Rusnak et al., 2004; National Research Council 2010]. *F. tularensis* is a gram-negative bacteria and intracellular pathogen that is endemic in wildlife populations in the temperate and boreal latitudes of North America, Europe, and Asia. There are currently four generally recognized subspecies [aka biovars, biotypes] of *F. tularensis* (*F. t. tularensis, F. t. holarctica; F. t. mediasiatica; F. t. novicida*), which exhibit characteristic differences in their virulence, ecological characteristics, biochemical properties, and geographic distributions [Vogler et al., 2009]. The subspecies *F.t. tularensis* is extremely infectious and virulent in humans, while subspecies *F. t. holarctica* and *F. t. mediasiatica* are associated with less severe disease in humans [Champion et al., 2009] The subspecies, *F. t. novicida,* is typically apathogenic in humans; however, and has been proposed for recognition as a distinct species taxon (i.e., *F. novicida*) on the basis of genetic sequence analyses [Larsson et al., 2009].

Incidence

The most virulent subspecies or biovar, *F. t. tularensis*, is widely distributed within North America, from Alaska and central Canada southward and into the eastern, central, western and southwestern regions of the US [Vogler et al., 2009]. A total of 1,368 cases of tularemia were reported in the US during the period from 1990 to 2000. Although *F. tularensis* is endemic and widely distributed across the US (see the distribution in figure 1), naturally-acquired human tularemia cases are relatively uncommon, except in a few focal outbreak localities where a few cases are seen annually, such as the island of Martha's Vineyard, Massachusetts. Nonetheless, confirmed cases of tularemia have been reported from all states except Hawaii [Brooks and Buchanan, 1970]. During the period 1990-2000, tularemia cases were documented from 44 states and approximately one in six of all US counties (543 of 3,143 counties nationwide: Hayes et al., 2002]. The island of Martha's Vineyard, Massachusetts, the site of the only two known outbreaks of primary pneumonic tularemia in the US, has developed into a major focus of human tularemia during the past decade [Feldman et al., 2001].

The principal reservoir hosts of *F. tularensis* in most areas are species of rabbits and rodents that use underground burrows and/or wetland habitats (cottontail rabbits, voles, ground squirrels, muskrats, beavers). However, infections have been documented in an extremely wide range of vertebrate and invertebrate taxa, including

sheep, deer, swine, minks, skunks, opossum, raccoon, birds (raptors, game birds), snakes, snapping turtle, ticks, flies, and mites [Kursban and Foshay 1946]. Tularemia infections can be caused by ingestion of contaminated water or animal flesh; contact with infected animals or animal secretions; tick or fly bites; and inhalation of aerosols. Although human tularemia infections in the US tend be most frequently associated with direct or indirect contact with wild rabbits and hares, this is not the case in all areas of the world. And, the possibility of transmission from other natural hosts, vectors, or environmental sources must not be overlooked [Kursban and Foshay, 1946]. Tularemia is thought to be have been accidentally introduced to the island of Martha's Vineyard during the 1930s, through infected cottontail rabbits from Arkansas and Missouri that were translocated to the island by hunting clubs.

F. tularensis is one of the most highly infectious known bacterial pathogens; inoculation or inhalation of as few as ten colony forming units of *F. t. tularensis* can cause potentially lethal disease in humans [Dennis et al., 2001]. Tularemia infections in laboratory workers can occur relatively frequently, because infections can be easily acquired during handling of infected specimens or cultures; and infections have occurred in laboratory personnel who were unaware that they have been exposed [Sulkin and Pike, 1951]. Three scientists suffered laboratory infections involving tularemia at Boston Hospital Medical Center that were not detected at the time they occurred, and, were only identified retroactively through serosurveys conducted during a biosecurity investigation that followed detection of tularemia contamination of a laboratory facility [Barry, 2005]. And recently, during November 2009, a laboratory infection from tularemia occurred in a scientist working with *F. tularensis* at the US Army Medical Research Institute of Infectious Diseases (USAMRIID) in Frederick, Maryland [National Research Council 2010; USAMRIID 2010].

Case Study
"How do you spell tularemia?"

This is direct quote of the response given by the duty nurse in the primary care facility of one the nation's premier hospital facilities in August 2006, when a patient, a retired military registered nurse, asked whether blood tests could be performed to determine if she might have contracted tularemia during a recent visit to Martha's Vineyard MA, an area where an ongoing tularemia outbreak was known to be in progress. The patient had traveled from Washington DC to Martha's Vineyard for a family wedding and had been out in wet grass, bare-legged and in sandals in an area frequented by rabbits, which are the principal reservoir for tularemia in Martha's Vineyard. The patient determined, through a targeted search of the United States National institute of Health website, that she had developed 10 of the 13 most characteristic symptoms of tularemia infection (Table 1).

The hospital nurse at this primary care facility evidently did not know what "tularemia" was, much less have any familiarity with the types of clinical presentations potentially associated with disease from this widely distributed and important infectious disease and bioweapon pathogen [Evans and Friedlander, 1997; Dennis et al., 2001; Darling and Woods, 2004; Hepburn et al., 2007].

Submitted 30 May 2010| Accepted 2 September 2010 | Revised 9 September 2010 | Published 17 September 2010

The case history of exposure and timeline of events that led up to this incident are summarized in Table 2. Despite describing her known history of recent exposure and symptoms, and informing the nurse that she had been directed by a trained medical professional to get tested for a possible tularemia infection, the patient was unable to obtain a clinical evaluation from the duty physician in the primary care ward, and was discharged by the duty nurse with instructions to "… *come back if you become really sick – and go to the Emergency Room*".

Public Health And Biosecurity Perspective

Tularemia is associated with a broad range of primary clinical presentations, and it is likely that many cases go unrecognized because the symptoms associated with *F. tularensis* infections are highly variable and nonspecific, even those associated with potentially fatal illness [Hepburn et al 2007]. The various disease syndromes and syndromes associated with human tularemia (cryptic, ulceroglandular, glandular, oculoglandular, oropharyngeal, typhoidal, pneumonic, septic), share overlapping symptoms in many instances (e.g., ulcerative topical lesions), but may also be cryptic or non-specific (e.g. "flu-like"). The type and severity of tularemia symptoms are mediated by the level of exposure and mechanism of infection (e.g., pneumonic: aerosol; oropharyngeal: ingestion; ulceroglandular: tick bite, skin contact with infected animal). Untreated tularemia may result in death, or a prolonged illness lasting for several months. Relapses have been reported among both untreated and treated tularemia patients [CIDRAP, 2010, and references therein]. Laboratory confirmation of tularemia infection may be quite difficult to achieve, because blood cultures from acute cases are rarely positive even in cases of severe disease, and there are significant impediments to obtaining definitive serological diagnoses [Hepburn et al., 2007].

What is particularly significant about this particular incident from the biosecurity and public health standpoints is that the hospital where this incident occurred is one of the nation's leading clinical medical facilities, and services a military and civilian community in the Washington DC metropolitan area that includes numerous personnel working with tularemia and other potential bioweapon pathogens in laboratory settings [USAMRIID 2010]. Personnel from this facility were actively involved in the epidemiological investigation of the 2001 anthrax letter bioterrorist attacks in Washington DC, and the facility has hosted terrorism attack and biodefense medical preparedness and training excercises. In addition, there had been two very high profile biodefense alert and response operations in the Washington DC area during the year prior to the time when the incident described here occurred, i.e.,

- detection of anthrax spores at postal facilities at the Pentagon and two other military-related sites in Washington DC area during March 2005, in which more than 1,000 people military and civilian personnel were placed received emergency antibiotic prophylactic treatment for suspected anthrax exposure [Department of Defense, 2005a, 2005b; GAO, 2006; RAND, 2006];
- recovery of tularemia bacteria from six different bioweapons sensors located in the vicinity of the US Capitol and the White House in Washington DC, in association with a mass antiwar protest rally involving more than 100,000 people that took place during the weekend of 24-25 September 2005 [Bush, 2009].

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The anthrax letter attacks of September/October 2001 demonstrated the importance of attention to detail and vigilance in considering any and all possibilities and potential patterns while interviewing and attending patients and when entering, reviewing, and cataloging patient records. Acts of terrorism may involve biological agents, toxic chemicals, or nuclear/radiological agents that exhibit cryptic or ambiguous clinical symptoms with long-delayed onset or incubation times. In cases in which a biological warfare agent is spread without warning, the event may be recognized only long after the fact when suspected or confirmed cases of unusual illnesses begin to be reported to public health agencies. Healthcare providers at all levels need to be provided with opportunities for developing familiarity with the clinical presentations typically associated with emerging disease pathogens and potential bioweapon agents, and latitude to exercise their intuition in recognizing disease syndromes that could be indicative of infection by a rare or unusual disease agent [Dembek et al., 2007].

It is encouraging to note that in the case study presented here, it was a dentist with training and experience and training in emergency response and forensic medical procedures who recognized that the mouth ulcers in his patient's mouth could be a symptom of systemic tularemia infection when coupled to other factors in his patient's clinical presentations, and recommended the patient seek immediate medical attention for this condition. This incident illustrates dramatically why all primary medical care personnel, as well as first responders and emergency medical personnel, need to be given the opportunity to become more familiar with the epidemiology and clinical symptoms of biological agents of greatest current concern – including, but not limited to, smallpox, anthrax, tularemia, plague -- and to be alert for potentially anomalous or unfamiliar combinations of symptoms that could point to unwitting exposure to novel or uncommon pathogens, biological toxins, toxic chemicals, or cryptic radiological agents [Dudley, 2003; Dembek et al., 2007].

Emerging and re-emerging disease pathogens that have the ability to infect humans and animals are exhibiting marked resurgences in many regions of the world, and not just in developing counties where public medical health infrastructures are either rudimentary or lacking entirely. The US, Canada, and European Union countries have seen increases in the frequency of animal-borne and tick-borne zoonotic diseases once thought to have been virtually eliminated as major public health concerns. In today's globalized world of high-volume, high-speed international air travel, physical distance can no longer be considered a measure of relative proximity to - or relative safety from – overseas outbreaks of diseases that affect plants, animals, or humans.

The resurgence of human infections from tularemia, anthrax, pneumonic plague, Congo-Crimean hemorrhagic fever, hantavirus, and other zoonotic diseases within human populations around the globe clearly demonstrates the need for establishing global disease surveillance and information systems that will facilitate the rapid reporting and field investigation of unusual disease clusters, potential outbreaks of emerging or re-emerging zoonotic diseases, and accidental or deliberate releases of bioweapon disease pathogens [Dudley, 2004, Ackerman and Gireaux, 2006; Dembek et al., 2007]. Newly emerging pathogens that can infect humans and animals are demonstrating the ability to spread rapidly around the world from small isolated epicenters in a single country, through international travel and trade networks.

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Outstanding recent examples of international dispersion of potentially fatal emerging pathogens include

- the emergence and rapid global spread of SARS virus through international air travel [Heymann 2004];
- monkeypox outbreaks involving 91 people in six US states which were ultimately traced to a single consignment of rodents imported from western Africa to the US through the exotic pet trade [DiGiulio and Eckburg, 2004; Hutson et al., 2007];
- transcontinental dispersal of West Nile Virus throughout most of the Western Hemisphere by migratory birds, over a period of less than ten years from the first appearance of this pathogen in New York City during 1999 [Artsob et al., 2009];
- rapid transcontinental dispersal of H5N1 highly pathogenic avian influenza from southeastern Asia into more than 60 countries in Asia, Europe, Africa, the Middle East through migratory birds and poultry industry supply chain networks [Dudley, 2008]

CONCLUSIONS

Nursing personnel, emergency healthcare responders, and physicians can only perform a crucial role in our first-line defense against bioterrorist attacks when they have been trained to recognize and investigate clinical syndromes and illness that may be indicative of possible exposure to biological agents or unusual disease pathogens.

Healthcare providers in all sectors and at all levels need to be provided with opportunities for developing familiarity with the clinical presentations typically associated with emerging disease pathogens and potential bioweapon agents, and given ready access to the laboratory diagnostic testing resources and technologies necessary to quickly and accurately identify disease pathogens that may be of importance to public health and national security.

ACKNOWLEDGEMENTS

Z.F. Dembek, D.A. Henderson, B.B. Saunders-Price, L. E. Peitersen, and three anonymous reviewers provided helpful comments on preliminary drafts.

J Med CBR Def | Volume 8, 2010
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TABLES

Table 1. Tularemia Symptoms.

TULAREMIA SYMPTOMS [NIAID 2005]	Symptoms Present in Patient
Sudden fever	YES
Chills	YES
Headaches	YES
Diarrhea	YES
Muscle aches	YES
Joint stiffness or pain	NO
Dry cough	YES
Weakness	NO
Mouth Ulcers	YES
Swollen and painful lymph glands	YES
Swollen and painful eyes	YES
Sore throat	YES
Red spot on skin that enlarges to an ulcer	NO

Table 1. List of principal symptoms of tularemia from fact-sheet published by the National Institute of Allergy and Infectious Diseases website [NIAID 2005]. The patient presented at the primary care facility in Washington DC with ten of the thirteen symptoms.

Table 2. Patient Case History and Timeline of Events

Date and Location	Description of Incidents and Events
27 July 2006 **Martha's Vineyard, MA.**	Local newspaper reports announcement by State Department of Public Health (DPH) that six cases of tularemia contracted during June and July have been confirmed from Martha's Vineyard. Newspaper report quotes DPH official as saying the symptoms of tularemia generally appear within several days to a week of infection, and that anyone with marked flu-like symptoms (fever, chest congestion, pain, lethargy; cough, chills) should seek medical attention. [Sigelman 2006]
29 July – 6 August 2006 **Martha's Vineyard, MA.**	Patient travels from Washington DC area to attend wedding celebration on the island of Martha's Vineyard. During outdoor festivities, patient was wearing sandals and walking on wet ground and wet grass because of daily rain showers.
	Patient observed rabbits on the property where wedding festivities were held, and during an outdoor Clam Bake held prior to the wedding.
	Patient sees reports in local media of at least six known cases of tularemia detected on the island during the previous few weeks.
	On day 4 of the visit (3 July), patient began exhibiting acute disease symptoms that included bombastic diarrhea, sore throat, laryngitis, non-productive cough, fever, chills, headache, muscle aches, and ocular discharge. Patient noticed that other guests at wedding also developed apparent conjunctivitis infections.
7 August 2006	Patient returns from Martha's Vineyard to home in Washington DC area.
8 August 2006, and days following **Washington DC metropolitan area**	Following return home on 7 August, patient develops mouth lesions. Given a prior knowledge of media reports of recent tularemia cases from the area, the patient searched National Library of Medicine's MedlinePlus for information about clinical presentations of tularemia, and read tularemia factsheet posted at http://www.niaid.nih.gov/factsheets/tularemia.htm
	Because the patient had had a dental procedure performed two weeks earlier, patient went to dentist to determine whether these mouth lesions could be abscesses from infections from the previous treatment.
	Patient gets emergency appointment with dentist, who tells patient

	that lesions are mouth ulcers, not abscesses, and that given the collateral symptoms observed and recent travel history, she should to go to hospital to be tested for a possible tularemia infection.
	Patient reports to Primary Care facility of major hospital facility in Washington DC area. Patient explains to duty nurse that reason for visit is to be evaluated for possible tularemia infection, based on compatible clinical profile, coupled with recent history of possible exposure in area with a known ongoing outbreak.
	Duty nurse consulted with the duty physician, and duty physician advised nurse to take patient's temperature to check for fever symptoms. Patient's temperature was determined to be "*within normal limits*".
	Patient discharged from primary care facility without ever being seen by duty physician, with instructions to report to the Emergency Room for evaluation and possible treatment in the event that more severe symptoms developed.

Table 2. Patient Case History. The timeline of exposure and symptoms for the patient in 2006. The patient was a retired military registered nurse, who had recently returned from a personal visit to Martha's Vineyard in Massachusetts.

FIGURES

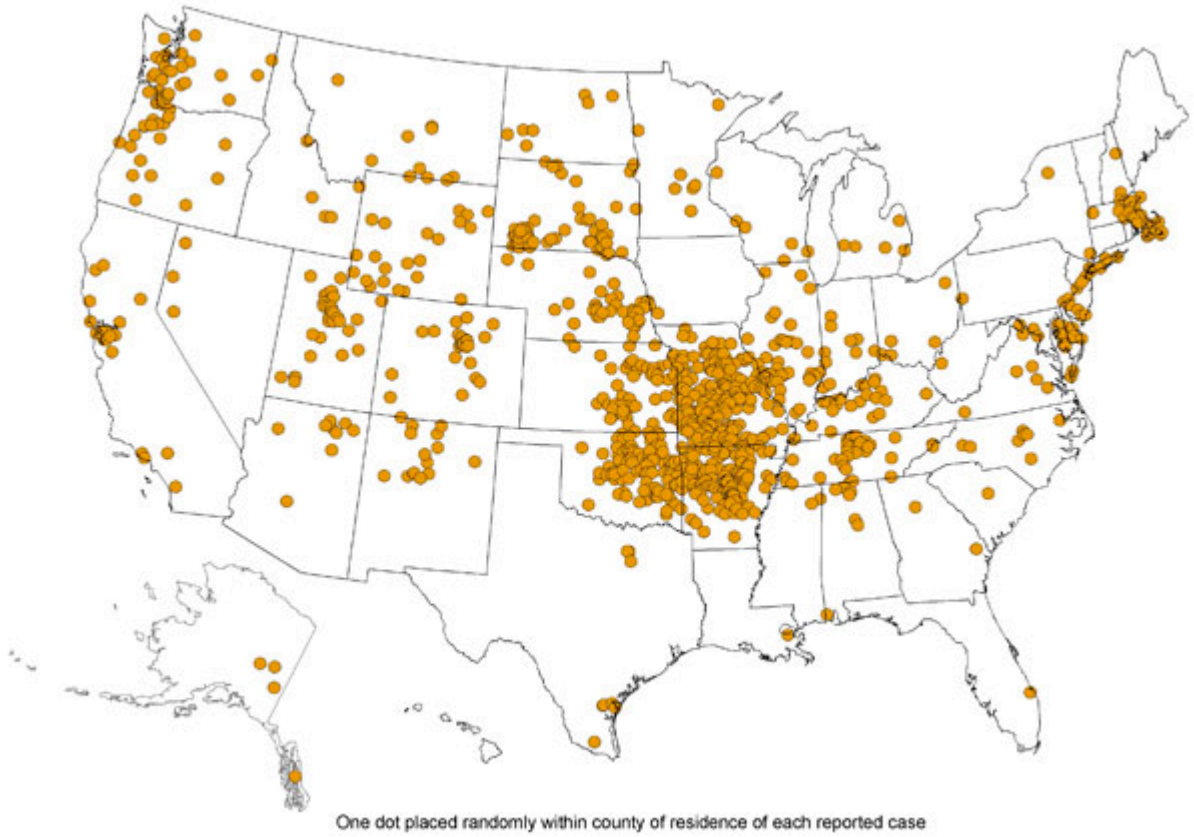

Figure 1. Locations of Reported Cases of Tularemia in the United States, 2000 -- 2008 [CDC 2010]

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