SYNDROMIC SURVEILLANCE FOR BIOTERRORISM-RELATED INHALATION ANTHRAX IN AN EMERGENCY DEPARTMENT POPULATION

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Objective: To utilize clinical data from emergency department admissions and published clinical case reports from the 2001 bioterrorism-related inhalation anthrax (IA) outbreak to develop a detection algorithm for syndromic surveillance. Methods: A comprehensive review of case reports and medical charts was undertaken to identify clinical characteristics of IA. Eleven historical cases were compared to 160 patients meeting a syndromic case definition based on acute respiratory failure and the presence of mediastinal widening or lymphadenopathy on a chest radiograph. Results: The majority of syndromic group patients admitted were due to motor vehicle accident (52%), followed by fall (10%), or other causes (4%). Positive culture for a gram positive rod was the most predictive feature for anthrax cases. Among signs and symptoms, myalgias, fatigue, sweats, nausea, headache, cough, confusion, fever, and chest pain were found to best discriminate between IA and syndromic patients. When radiological findings were examined, consolidation and pleural effusions were both significantly higher among IA patients. A four step algorithm was devised based on combinations of the most accurate clinical features and the availability of data during the course of typical patient care. The sensitivity (91%) and specificity (96%) of the algorithm were found to be high. Conclusions: Surveillance based on late stage findings of IA can be used by clinicians to identify high risk patients in the Emergency Department using a simple decision tree.

Implications for public health: Monitoring pre-diagnostic indicators of IA can provide enough credible evidence to initiate an epidemiological investigation leading to earlier outbreak detection and more effective public health response.

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PREFACE

This dissertation is dedicated to the memory of Rita A. Soulakis

1.0 INTRODUCTION

The mission of public health is to protect and promote the health of the community. In the United States, treatment and prevention of major chronic conditions such as cardiovascular disease commands the majority of resources. Further resources go to the tracking and investigation of infectious diseases, making the environment safe, combating obesity, and assuring the mental and social health of the community. In the wake of the terrorist attacks of September 11th 2001, Emergency Preparedness emerged to share the list of top priorities for public health. The chaos that ensued following the attacks, the loss of thousands of lives, and the disruption of services to the attack sites highlighted the need for well-coordinated and efficient services to deal with the unexpected. In 2013, the US Health and Human Services budget for Emergency Preparedness will be 4.5 billion dollars across all Departments. (1)

Terrorists perpetrate acts of violence or intimidation to further their ideology or beliefs. The hallmark of terrorism is to use small, focused acts affecting a small area or region to sow fear in the greater population. Bioterrorism is terrorism employing biological agents. Only days after the World Trade Center towers fell, the deadliest act of domestic bioterrorism on American soil brought bioterrorism into focus for public health. Unknown persons mailed anthrax tainted letters to headquarters of media outlets and offices of the US Senate creating havoc at each stop along the way. (2)

Anthrax is a Category A agent on the CDC's list of Critical Biological Agents because of its ease of dissemination, high mortality rate, potential major impact on public health, ability to incite panic and social disruption, and the requirement for additional major public health measures. (3) Other agents in Category A include smallpox, plague, botulism, tularemia and viral

hemorrhagic fevers. Category B agents, such as Q fever, brucellosis, and encephalitis, also have some potential for easy dissemination with resultant illness, but generally cause illness and death, with the exception of Brucella. Thus most Category B would be expected to have lower medical and public health impact than Category A. Of the Category A agents, experts often cite anthrax as the most suitable for a large scale attack. Smallpox is deadly but obtaining the agent is difficult and even the smallest release have the potential to decimate an entire population because of its communicability. Plague, botulism and tularemia can also decimate a population but the wide availability of effective treatment and prophylaxis limit their threat. Viral hemorrhagic fevers appear to pose a threat but no known development of weaponized agents exists. (4) Anthrax is known to exist in a bioweaponized state for the specific intent of military attack. Tests have been conducted by Iraq and the former Soviet Union. A recent analysis reports that there is clear evidence of or widespread assertions from nongovernmental sources alleging the existence of offensive biological weapons programs in at least 13 countries. (5)

In 2001, intentional release of aerosolized anthrax powder through the US Postal Service led to 11 cases of inhalation anthrax; six of which were fatal. Stress and anxiety gripped Americans as it seemed anthrax tainted letters could appear at anytime, anyplace. Tens of thousands Americans completed full courses of prophylactic antibiotics. (7) In the wake of the anthrax letters, millions were spent to disinfect and decontaminate postal facilities as well as offices on Capitol Hill. Public health agencies monitored emergency departments around the clock to maintain vigilance that a case resembling anthrax may arise. Public health agencies also spent valuable resources sifting through hundreds of cases of febrile illness detected by their existing syndromic surveillance hoping to gain awareness of the earliest signs of a second, much larger, anthrax attack.

This study seeks to investigate the effectiveness of a syndromic surveillance approach for monitoring bioterrorism-related anthrax. The project will specifically 1) examine the value of using co-occurrence of acute respiratory failure and widened mediastinum for inhalation anthrax surveillance; 2) establish a baseline of this respiratory failure/widened mediastinum syndrome in an emergency department population; and 3) using a systematic analysis of the anthrax cases of 2001, simulate what a bioterrorism related outbreak would look like.

A major problem in the study of syndromic surveillance is that the focus on sensitive systems often leads to false alarms of positive events. As such, investigators developing systems for anthrax surveillance primarily monitor for large outbreaks resembling seasonal influenza. This study was designed to advance research in the field of syndromic surveillance for inhalation anthrax in an emergency department population by focusing on a different approach. The primary aim of this study is to examine how syndromic surveillance accuracy and timeliness may be improved by the use of fulminate phase indicators of anthrax.

2.0 PUBLIC HEALTH SIGNIFICANCE

Anthrax is important as a disease of agriculture and industry as well as a biological weapon. Intentional release of aerosolized anthrax spores resulted in twenty two cases of anthrax in 2001. The spores were enclosed in envelopes and then mailed to media companies and offices of the US Senate. This act of bioterrorism resulted in 11 cases of cutaneous anthrax and 11 cases of inhalation anthrax with 6 of those cases resulting in death. (6) Although the total number of anthrax cases represents a tiny fraction of the US population, the implications for the nation were extensive, in part because the letters "leaked" in transit and infected (and killed) postal service employees and at least one seemingly random individual through their home mail. Investigation, prophylaxis, and cleanup cost millions of dollars. In addition, the event created a sense of terror for millions of American citizens. The public health significance of early warning systems for bioterrorist attacks is placed into context below as the magnitude of the public health response in 2001 is reviewed.

2.1 PROPHYLAXIS

Beyond those persons directly infected with anthrax, the incident had far greater reach. Preventive measures had to be taken for thousands of persons who were potentially exposed to anthrax. It is estimated that over 10,000 persons across the Eastern United States were offered >60 days of post-exposure antimicrobial prophylaxis. (7) Surveys were administered at 10- and 30- day refill clinics. Some 6,178 persons completed surveys or interviews. Of the 5,343 persons

who reported taking at least one dose of antimicrobial prophylaxis, 57% (n=3,032) reported adverse events. Nausea or vomiting (27%), headaches (25%), and dizziness (22%) were commonly reported. 14% of the respondents graded their adverse event as "severe." The Anthrax Vaccine and Antibiotic Availability Program reported 12 serious adverse events (SAE). SAEs were defined as "any untoward medical occurrence that may have resulted in any of the following: death, life threatening event, inpatient hospitalization, persistent or significant disability or incapacity, and/or congenital anomaly or birth defect." (8) Hypersensitivity pneumonitis following anthrax vaccination was documented in a 39-year old previously healthy man on active duty in the Marines. (9)

In Washington, D.C. 2,000 workers were advised to complete 60 days of post exposure prophylaxis to prevent inhalation anthrax. (10) Later surveys of the group (N=251) would show 98 (40%) reported full adherence, 45 (18%) discontinued prophylaxis and never restarted, and 102 (42%) reduced the dosage, forgot a pill the previous day, or stopped their antimicrobial therapy and restarted at least once. Two of the most cited reasons for stopping or reducing their dosage were adverse effects – 73/102 (78%) -- or potential for long-term adverse effects – 59/102 (63%). In Connecticut, over 95% of 1,122 postal workers at Connecticut distribution Center was given post-exposure prophylaxis. Investigators collected 485 nasal swabs but no anthrax was isolated. (11)

In New York City, one hundred members of 5 disaster medical assistance teams and other health professionals were deployed within 18 hours of activation. Over a 68-hour period, 7,076 patients were evaluated; representing all postal employees in the 6 major postal facilities in New York believed to be at risk for anthrax exposure. Of the total, 2,452 patients were seen during the first 24 hours, 3,875 during the second 24 hours, and the remaining 749 during the last

20 hours of operations. An average of 161 employees was screened per hour. The antibiotic most commonly dispensed was ciprofloxacin, followed by doxycycline and amoxicillin. (12)

On October 12th, diagnosis of cutaneous anthrax was confirmed in a New York City media company staff member. Between Friday, October 12, and Tuesday, October 16, after approximately 42 hours of operation and an average of 55 staff persons per shift, 1,322 persons were briefed, completed epidemiologic and law enforcement interviews, underwent medical assessments, had nasal swabs taken to better define exposures, and were given a 14-day supply of antibiotics within the point of distribution (POD) space. (13)

In addition to those with occupational exposures, the general public with perceived risk of anthrax exposure sought medical care. Surveys of emergency medicine physicians showed that patients self-identified as at-risk for inhalation anthrax were approaching doctors for antimicrobial prophylaxis during the 2001 attacks. (14,15)

2.2 STRESS AND ANXIETY

Terrorism directly impacts public health by giving rise to fear among citizens concerned with future attacks. Considerable distress and the onset of clinical disorders such as post traumatic stress disorder and depression followed the 2001 anthrax attack. Dougall et al. recently attempted to measure the extent to which a random sampling of people in Allegheny County were distressed or bothered by symptoms of intrusive thoughts, avoidance, and hyper arousal following media coverage of the anthrax attacks. Initial anthrax media exposure was shown to be related to distress. The amount of anthrax media coverage participants watched at the onset of the attacks predicted anthrax-related stress, intrusions, and avoidance symptoms. (16)

It is clear that Americans were disturbed by the possibility of exposure to inhalation anthrax. In Idaho, the State Emergency Medical Services Communications Center (StateComm) received 73 routine hazardous materials calls and no biohazard calls from August 1st to October 7th. From October 8th to December 31st, StateComm received 53 routine hazmat calls and 133 biohazard calls; all biohazard calls were related to suspicious powders. Each call required the involvement of public health officials, law enforcement including FBI, and hazmat. All powder related incidents were treated as potential criminal acts, and all samples were maintained as evidence. In many cases, if the envelope or package had a return address, the sender was contacted immediately by authorities, probably to their great shock, to verify the contents did not contain biological contaminants. (17)

Panic was felt at every level of public health. In the early days of the anthrax attacks, the CDC formed an agency wide Emergency Operations Center (EOC) to assist in coordinating the response to calls from the general public, clinicians, and public health departments. From October 8 to November 11, 2001, a total of 11,063 telephone calls were documented and responded to by EOC telephone bank staff. The most frequently mentioned topic was "questions about the availability of an anthrax vaccine" (2,438 [58.4%] of 4,178 calls), followed by "request for general bioterrorism information" (617 calls [14.8%]), "request for information about personal protective equipment" (501 calls [12.0%]), "general concerns about bioterrorism" (491 calls [11.8%]), and "request for information about smallpox" (400 calls [9.6%]). (18) Call volume increased to a peak of 858 calls received on October 16, 2001, shortly after the public announcement that a letter containing anthrax had been opened in Senator Tom Daschle's office.

2.3 ENVIRONMENTAL INVESTIGATIONS

After the intentional anthrax release, public health agencies incurred a major cost due to investigating all potentially contaminated facilities as well as the subsequent cleanup of those facilities. On October 18th, 2001 a suspected case of cutaneous anthrax was confirmed in a postal worker from the Trenton Processing and Distribution Center where at least four suspect letters were postmarked. From October 18th – November 3rd 2001 a total of 57 facilities in New Jersey were environmentally sampled by a team consisting of the New Jersey Department of Health and Senior Services, the Federal Bureau of Investigation, and the CDC National Institute for Occupational Safety. (19) A total of 1369 samples were collected with positive sample results found in two mail processing and distribution centers, six municipal post offices, and one private company. In order to enter a contaminated facility, investigators were required to wear Saranex full-body protective suits with hoods, disposable rubber boots, two pairs of nitrile gloves, and full-face powered air-purifying respirators with high-efficiency filters. When investigators exited a contaminated building they passed through a decontamination procedure, which included being sprayed twice from head to foot with 10% solution of sodium hypochlorite followed by a water rinse before removing their suits, boots, gloves, and respirator. (20) The cost of remediation of *Bacillus anthracis* contamination in the U.S. Department of Justice mail facility, one of nine facilities with a positive result in the New Jersey area, was reported to be $463,916. (21)

3.0 EPIDEMIOLOGY OF ANTHRAX

This review will provide an analysis of statistics, trends, and outbreak reports from the literature which illustrate the common sources and exposures of anthrax over the last 120 years. An analysis of the literature will provide evidence of how the epidemiology of anthrax has shifted based on what was common epidemiological phenomenon in the United States to what is a current public health threat today.

3.1 NATURAL HISTORY OF BACILLUS ANTHRACIS

B. anthracis is the etiologic agent of anthrax. It is a gram-positive, nonmotile, aerobic, spore forming, rod shaped bacterium with a centrally located spore. The spore is approximately one micrometer (1μm). (22) Anthrax spores in their dormant state are highly resistant to adverse environmental conditions including heat, ultraviolet and ionizing radiation, pressure, and chemical agents. Spores can survive for years in contaminated soil. Anthrax spores can enter the body through the mouth, respiratory tract, or through breaks in the skin causing gastrointestinal, inhalational, or cutaneous anthrax respectively. Once a spore encounters a suitable environment such as the circulatory system of a living host, it will return to vegetative growth. Experimental evidence indicates that vegetative cells of *B. anthracis* have specific nutrient and physiologic requirements and survive poorly outside the host. The entire life cycle of *B. anthracis* appears to occur within the host. (22)

In nature, anthrax is a disease of grazing animals. Herbivores consume spores through grazing, wallowing, or other close contact with soil. The spores germinate to produce the vegetative forms which multiply and express their virulence factors. The effect is typically lethal. The bacilli are shed by the dying or dead animal through the loss of blood. (25) Bacilli shed by the dying animal will sporulate on contact with air. (23) The presence of specific nutrients in the soil such as calcium helps to maintain the viability of the spores in the environment for longer periods of time. (24)

Dissemination of anthrax spores can occur in many ways. When a host dies, the carcass can be opened by scavengers, introducing vegetative cells to the environment where nutrients are limited and sporulation can occur. Carnivores are less susceptible to the disease and can ingest the spores without developing the disease. They can act as carriers by dispersing ingested spores over large areas but vegetative cells do not survive passage through the scavenger's stomach. Avian scavengers, like vultures, can spread spores even further. Dragon et al have found that viscera attached to fur, wind and water, or feces all work to distribute spores into the environment. (25**)** However, even light scavenging is enough to release concentrations of *B anthracis* vegetative cells from the body to microenvironments conducive to the formation of spores, resulting in significant contamination of the immediate environment. (25) Cycles of rain and drought concentrate spores in low areas where calcium rich sediments are deposited creating 'storage areas' where favorable environments exist for long periods of time. (26)

Epizootics occur when animals ingest anthrax spores through grazing in contaminated fields. Environmental factors, such as droughts, may require animals to graze more closely to the ground, ingesting more of the contaminated soil especially in storage areas. Breeding behavior may also lead to infection. Dragon found that rutting aggression of male bison, bulls, such as

increased stamping and wallowing may greatly increase their chance of exposure to anthrax spores. In storage areas, this behavior can create large dust clouds of aerosolized spores. The spores enter the bulls' respiratory tract through normal breathing or snorting, a common rutting behavior. This behavior may also explain the high fatality of anthrax infected bulls versus female bison which do not have the tendency to inhale as many spores Anthrax is more lethal when inhaled than when ingested by herbivores. Cutaneous anthrax is infrequent among herbivores.

3.2 INCIDENCE OF REPORTED ANTHRAX CASES IN HUMAN POPULATIONS

Fortunately, anthrax occurs less frequently in human populations, than in animal populations. In addition, our knowledge of anthrax, its transmission, and its risk factors have led to a significant decline in the incidence of anthrax outbreaks in the United States over the past 200 years. To illustrate, at the beginning of the 20th century, anthrax claimed the lives of many Americans. From 1865 to 1906, 128 deaths from anthrax were recorded on death certificates for the state of Massachusetts. (27)

Table 1. Incidence of Reported Cases in 1919 in US Cities with Population > 100,000

City	State	Population (k)	Cases	Deaths	Cases/100k	Deaths/100k
New York	NY	5,580	14	9	0.3	0.2
Philadelphia	PA	1,810	10	4	0.6	0.2
Boston	MA	740	4	0	0.5	
Camden, NJ	NJ	120	3	1	2.5	0.8
Wilmington	DE	110	3	0	2.7	
San Francisco	CA	500	3	0	0.6	
Denver	CO	250	2	1	0.8	0.4
Atlanta	GA	200	2	0	1.0	
Hartford	CT	140	1	1	0.7	0.7
Portland, OR	OR	256	1	1	0.4	0.4
Reading	PA	100	1	0	1.0	
Worcester	MA	180	1	0	0.6	
Baltimore	MD	720	1	0	0.1	
Detroit	MI	970	0	1		0.1
Milwaukee	WI	450	0	1		0.2
Chicago	IL	270	0	1		0.4
Des Moines	IA	120	0	1		0.8

The first public health systems for surveillance of anthrax began when *Public Health Reports* started publishing a regular report on anthrax in 1912. (28) Although Congress enacted a law in 1902 directing the Surgeon General to provide forms to all state health officers for the collection and compilation of data and for the publication of the reports at a national level, it was not until 1912 that timely reports were mandated by telegraph for five diseases and the monthly reporting, by letter, of ten additional diseases. Anthrax was included in the monthly reporting group. Incidence of occupational disease in large American cities in 1919 is shown in **Table 1** with a case fatality rate (CFR) of 46%**.** (29) The table highlights that anthrax was not an uncommon health issue, and a highly fatal one, at the turn of the century.

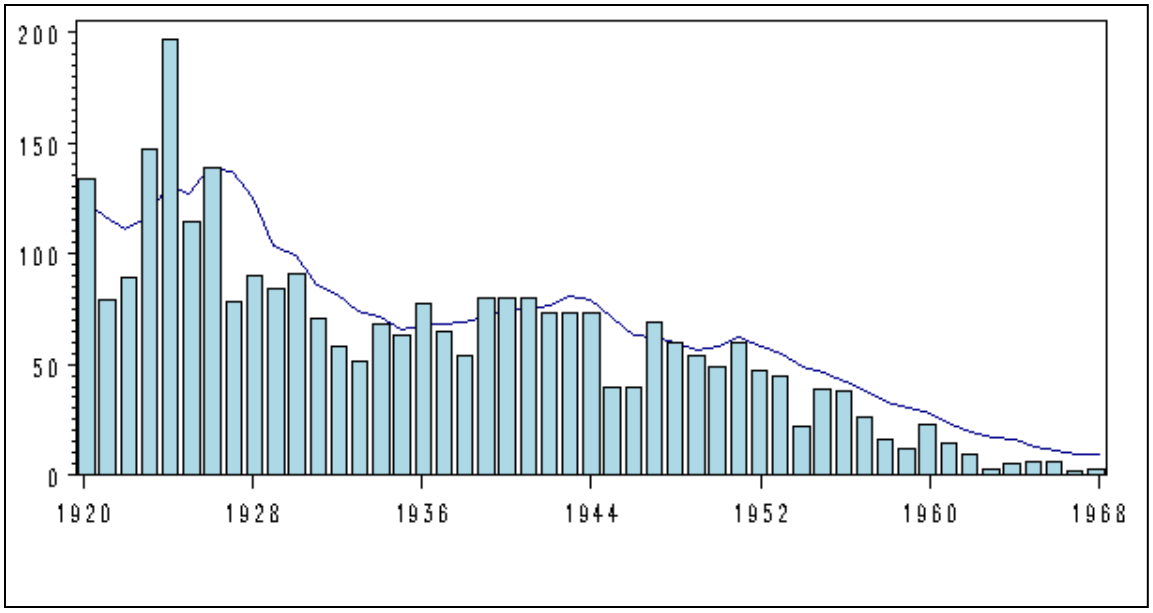


Figure 1. Incidence of Reported Cases of Anthrax, United States 1920-1968

From 1919-1925, 33 states reported 632 cases of anthrax with 177 deaths (28% CFR). The peak year for the interval was 1920 with 115 cases and 43 deaths (37% CFR). The three states with the highest incidence of reported cases during the interval were all located in the Northeast United States, states with high industrial exposure in mills and tanneries: PA; 104 cases/15 deaths, NY; 67 cases/29 deaths, and MA; 62 cases/7 deaths. Other states with a high incidence of reported cases were CO (55 cases), OH (13 deaths), IL (15 deaths), and LA (12 deaths). (30) States with the highest single year incidence of reported cases during this period included: 1919 MA (22 cases), 1920 NY (24 cases), 1924 TX (32 cases), 1919 NY (11 deaths), 1920 New Jersey (7 deaths). (30)

The US Public Health Service received an average of 60 anthrax reports a year from 1920 to 1968. In **Figure 1,** the annual incidence of reported cases as noted by Cowan, Glassman, and McNabb is plotted over time with the five year moving average plotted in blue. (32,33,34) The

peak annual incidence was 197 cases in 1924. Twenty seven deaths from anthrax were reported in 1924. (31) The most common form of anthrax affecting individuals in this time period was cutaneous anthrax, with less than 17 cases of inhalation anthrax reported in the literature for the time period. Gastrointestinal anthrax has only been occasionally referenced in the US literature in the last century, but no case reports have been published. (32,33,34).

Incident reports of human cases of anthrax frequently have originated from agricultural settings. From 1945-1951, Steele reported 372 anthrax cases in the United States, 29 due to agricultural exposure: 21 farmers and 8 veterinarians. (35) From 1957-2001, Bales reported seven CDC investigations of anthrax outbreaks in agricultural settings in the United States. (36) Anthrax in agricultural settings in the US occurs most frequently in ND, SD, MT, MN, and TX where it is enzootic.

Industries such as leather goods manufacturing and textiles also had a high reported incidence of anthrax in the early 20th century. Experts also regard the reporting of industrial anthrax cases as being more complete than in agricultural settings due to federal reporting regulations for workplace safety as well as the monitoring of claims for worker's compensation by the State Departments of Labor. (37) Industry-related anthrax in the early 20th century was largely centered on the Northeastern states of US: NY, PA, MA, NJ, and NH. These states are often referred to in the literature as 'tannery' states, given the high number of industrial cases in this region. (29) Many tannery states, e.g. MA, NJ, NY, PA, reported anthrax cases to federal authorities every year until 1963. (38)

In the early 20th century, reported anthrax cases were fairly frequent. From 1919-1924, 439 occupational cases of anthrax with 107 deaths were reported. The maximum number of these cases were from Pennsylvania (n=102) and the maximum number of deaths were noted in

NY (n=22). As time progressed, the frequency of reported anthrax declined. (39) From 1927-1929, the US recorded 162 cases, 30 deaths in 48 states and the District of Columbia. The highest cases/fatalities for the reporting period were MA 20/1, NY 37/6, and PA 29/8. (38,35)

Table 2. Incidence of Reported Anthrax Cases by Material and Industry 1899-1943

Period		Leather		Wool		Agriculture		Hair		Total	
		Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
1899	1904	86	21	88	23			70	17	261	67
1907	1919	111		7		1		5		126	
1919	1925	147		17		68		40		632	
1927	1929	48	5	43	4	21	7	10	3	113	
1934	1938	97	7	51	3	94	19			357	52
1939	1943	79	9	237	8	65	10			408	33

The incidence of reported anthrax cases by industry from annual reports on industrial anthrax of the Industrial Hygiene Section of the American Public health Association is given in **Table 2**. (30,37,38) Blank cells represent gaps in reporting for which data was not available. These reports were primarily due to the work of H.F. Smyth, a professor of industrial hygiene at the University of Pennsylvania School of Hygiene and chair of the committee. Smyth would tirelessly survey state and local health departments, hospitals, physicians, employers, and occasionally patients. Across all industries, reported anthrax cases are concentrated, as discussed above, in the leather, wool/tannery, and agricultural industries. Anthrax due to exposure to animal hair had the highest case fatality rate from 1899-1943 with 20/55 cases being fatal. Death reports were not available for all years. The primary reason for a high level of anthrax cases in the leather and wool industries is the potential for anthrax spores to be carried into the facilities through the hides and hair of the animal products being processed there. Osborn conducted an exhaustive investigation of the origin of all infected materials resulting in anthrax in MA over

the three year period (1916-1919); one of the highest incident periods in US history. The results are summarized in **Table 3.** (27) Most of the hides and hair bearing anthrax spores were not from US-based animals, but rather hides and hair from animals from other foreign countries.

Table 3. Incidence of Anthrax Cases by Source and Infected Product in MA from 1916-19

Country	Hides	Hair/wool
China	71	
Argentina	17	6
India	16	
United States	5	2
Brazil	3	
Venezuela	1	
Russia	0	7
Mexico	0	1

Over time, public health interventions have been successful in reducing the frequency of contact with anthrax in human populations. Vaccines and federal regulations have been developed and implemented to stem the number of industrial anthrax cases. Today, the frequency of anthrax in humans in the United States is sporadic, as illustrated in **Figure 2**.

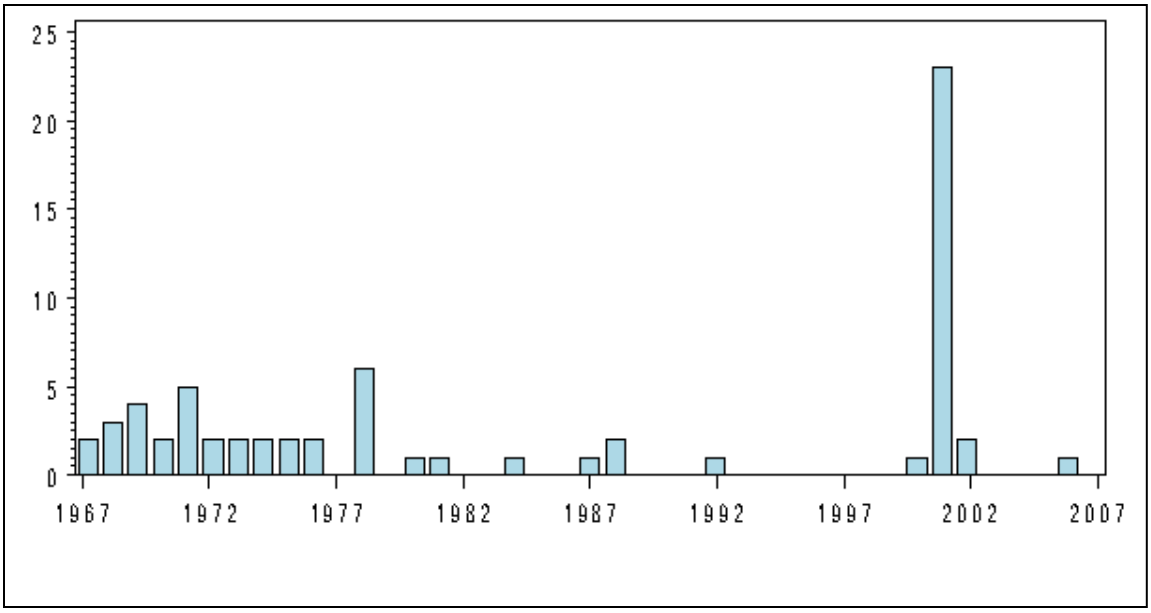


Figure 2. Incidence of Reported Cases of Human Anthrax, United States 1967-2007

There were no reported deaths attributed to anthrax from 1979-2000. (40,41) From 2000-2007, only 5 naturally occurring cases of anthrax were reported in the United States. (33) The few cases which occur are largely farm and agriculture related cases, or involve rare and exotic exposures. (30,38,37) Thus, the burden of naturally occurring forms of anthrax in humans has become a small health concern in the United States. Although anthrax incidence has dramatically declined in the US, the human anthrax remains an international problem.

Table 4. International Incidence (in Thousands) of Reported Anthrax Cases from 1924- 1953

	1929	1932	1935	1938	1941	1944	1947	1950	1953
Bulgaria			1				1.5		
Iran					2.3		1.5		
Italy	2	1.6	1.2	1.1			1.7	1.2	1.1
Portugal								2.2	1.3
Turkey							1.4	1.4	1.5
USSR	15	4.5	2.5						
Yugoslavia								1.1	1.1
Romania			1.2	2.2	1				
Spain								1.6	1

Glassman presents epidemiological data extracted from the statistics by the Health Organization of the League of Nations for the years 1924-1938 and by the World Health Organization for the years 1939-1953 (34) (**Table 4**). Hugh-Jones also describes the global anthrax problem today. As of 1996, several countries still report regular human anthrax cases: China - 898 cases, Tajikistan - 105, Azerbaijan - 76 cases, Kazakhstan - 70 cases, Kyrgyzstan - 54 cases, and Spain - 50 cases. Hyper-endemic anthrax also still exists in many countries around the world including India, Pakistan, Afghanistan, Turkey, Iran, Iraq, Peru, Argentina, Ecuador, Mexico, and Panama. (42) Existing levels of anthrax in international settings are lower than existed early in the century. This observed reduction in anthrax cases is largely attributed to enhanced surveillance and livestock vaccination programs.

While reductions in anthrax frequency internationally are apparent, anthrax may exist as a larger problem than is evident through current reporting systems. Although many physicians are trained to identify and treat anthrax, reporting procedures may not be enforced especially in rural regions of lower income areas.

3.3 RURAL AND AGRICULTURAL EXPOSURES TO ANTHRAX

Agricultural sources of anthrax exposure, through close contact with sick animals, account for a high proportion of the total human anthrax cases for most of the world. The rarest transmission is to a human from a live animal. A more common source of exposure is for farmers, who, unaware of their risk, handle animals which have died suddenly from anthrax. Grazing and feed practices are the primarily issues involved in outbreaks of anthrax in livestock. Farmers may graze cattle, pigs, horses, goats, or sheep in contaminated fields. Farmers may also unknowingly use contaminated bone meal feed. (32) Sick animals are then slaughtered, skinned, and/or butchered by agricultural workers. Abrasions, open wounds, or other breaks in the skin of farm workers can lead to cutaneous anthrax. Occasionally, veterinarians may contract anthrax from handling an animal for a post mortem inspection. Unsuspecting butchers may also be asked to process meat of an animal which died suddenly. Inhalation anthrax in humans has been rarely reported in agricultural settings except for circumstances where dust generated by contaminated bone meal fertilizers has been used.

Although it does not occur with great frequency in the US, human anthrax infection in agricultural and rural settings does occur regularly in many countries. For instance, Ozkurt reported that 503 cases of human anthrax occurred in rural Eastern Turkey from 1992-2004; averaging 38.6 per year with a maximum of 50 cases. 99% of all cases were cutaneous anthrax, with some rare gastrointestinal cases. Only 2 cases died. 100% of patients had a history of exposure to anthrax-infected animals. (43)

Peck reports that from 1992-2002, 87 cases consistent with cutaneous anthrax were reported at Albert Schweitzer Hospital in Haiti with seven deaths; 58 (66%) of the individuals affected were less than sixteen years of age. (44). Children in Haiti play an important role in

butchering animals. Elsewhere child anthrax is infrequent to rare. Peck describes rural anthrax exposure among children: “Butchering of animals in Haitian society is often performed with the assistance of children and involves close contact between the face of the butcher and the hide of the animal”. In a common butchering practice, the butcher blows into a small incision made into the hide of the cow to aid in the removal of the hide. Practices such as these may partly explain the high incidence of cutaneous anthrax in children and location of many of these lesions on the face.”

Irmak reports that 39 patient admissions due to anthrax occurred at University Medical Center in Turkey from 1996-2002. 17 patients resided in the city; 22 in rural surroundings. 100% of the patients had a history of handling livestock or slaughtering or processing, skinning or cutting meat from an allegedly sick animal. 100% of the cases were cutaneous anthrax. (45)

From 1967-2002, 71 cases were admitted to National Hospital of Peru with a diagnosis of anthrax; 100% of the cases were cutaneous anthrax. (46) Cases were distributed according to the following exposures: 28/71 agricultural; 17/71 cattle raising; 10/71 meat handling. Of these 66/71 patients reported their source of exposure; 34 patients came into contact with animal during slaughter; 26 had direct contact with meat only. Cases of human anthrax were associated with the following animals: beef cattle 56/71, goats 10/71, and swine 5/71. The Peruvian General Office of Epidemiology reported a decrease from an average of 300-350 cases per year in 1980s to 50 per year in 2000’s.

In rural settings, food preparation practices can sometimes lead to human anthrax. In Lebanon, rural livestock is often not vaccinated contributing to occasional epizootics. It is customary to slaughter sick animals. From 1960-1974, hundreds of cases of human gastrointestinal anthrax cases occurred in Bekaa Valley in Lebanon; where the consumption of

raw or poorly cooked meat is customary. (47) One outbreak involved a family which consumed a goat that was slaughtered because it was dying. Meat was consumed raw by friends and family. The farmer's wife died and her sister developed cutaneous anthrax on her lip.

A near-outbreak in the US was reported in the MMWR in 2000. (48) In August, the Minnesota Department of Health was notified of a positive isolate for *B. anthracis* from a specimen taken from one of five cattle which suddenly died. A farmer reportedly killed, gutted, and skinned, one of those five cattle that were "unable to rise". The local veterinarian had mistakenly approved the animal for slaughter, and 6 family members ate the meat over 20 days. Although two family members experienced gastrointestinal illness, no one developed anthrax.

3.4 INDUSTRIAL EXPOSURES TO ANTHRAX

Industrial anthrax comprises the highest historical proportion of the disease in humans in the United States. While most cases of agriculturally related anthrax are due to local exposure to anthrax, most cases of industrial anthrax are due to the importation and processing of contaminated materials from regions of the world with high rates of anthrax. Spores can be found on dried or pickled cow hides, goat skins, horse hair or wool. (27) Often inspection standards are low in developing countries. The result is that factories processing large amounts of imported hides, hair, wool and other materials receive substandard materials.

Industrial settings provide an environment with repeated exposure to highly contaminated materials. For half of the 20th century, inadequate methods of decontamination, lack of safety equipment, and poorly ventilated facilities contributed to a high number of anthrax cases among workers. The demographic profile of industrial workers was reflected in the incident anthrax

cases– male, working age. Most cases were cutaneous, rarely inhalational. For example, Osborn reported 113 of 126 cases due to industrial setting in Massachusetts. All cases were cutaneous. (27) In 1951 the National Office of Vital Statistics Public Health Service reported a total of 60 cases; 45 in the Northeastern US probably related to industry. (35) Secular trends also contribute to the incidence of anthrax. Wars (WWI, WWII) and the Great Depression lead to importation of low quality goods. (30)

Handling hides offers an opportunity for infection if the worker has an abrasion, scratch, or cut. Unbroken skin is adequate protection from anthrax. (27) From 1914, war time, the number of imported hides from Asian countries (China, India, and Pakistan) and South America (Argentina, Brazil, and Venezuela) increased. As the quality of hides decreased, anthrax incidence increased. (27) From 1921-1922, depression increased importation of inadequately disinfected hides. (30) There were many contributing factors leading to anthrax in the leather industry. Disinfection was inadequate, injured hides, and created expense to the mill to locally disinfect. Consular certificates assuring area 'anthrax free' could be obtained illegally. (27) It was hard to sample bundles of materials at the port of entry. Most large shipments of hides were likely to have some anthrax. However, it was difficult to show the total amount per bundle. Industrial shipping seasons affect the shipping and storage of hides and other materials which can increase spore contamination. (27)

From 1916-1919, MA reported 17 cases of anthrax in freight handlers: Teamsters, longshoremen, and hideweighers (3,10,4). They would come into contact with infected hides when unloading hides from ships or shifting them about the docks. Although it is possible wool or hair could infect the freight handlers, in every case in MA, it was hides. The international freight industry also is at risk for developing anthrax. Cole published his findings from a 1949

study of hide porters in Dar es Salaam, Tanzania. (49) Dar es Salaam is the main channel of export for TZ and East Africa. In 1949, 28 cases admitted to ID section of DES Hospital; in 1950 over 27 cases by July.

The wool industry has garnered the most attention due to the increased risk of fatal inhalation anthrax. Greenfield (1880), Legge (1905) and Eurich (1913) all provide summaries of inhalation anthrax in the wool industry in England. (50,51,52,53,54,55,56) Very high mortality led England to pass disinfection regulations. US public health officials noted that since England opened disinfection stations, the US began to receive more inferior wool because of the disinfection charge and lack of a European market for inferior materials. (57) A contemporary survey is provided by LaForce in 1978. The US wool industry developed later than its UK counterpart. It was not until the second decade of the 20th century that reports of industrial anthrax in the wool industry were published in the US. Osborn reported from 1916-1919, 3 of 126 cases in MA were inhalation anthrax. (27) Smyth and Cheney later reported that in NY, 23 of 37 cases related to wool handling. (38)

Secular trends can infect the incidence of anthrax. Smyth reported that for Philadelphia, after the start of WWII, anthrax incidence tripled. Analysis of anthrax in Philadelphia by source of infection showed only one case increase. However, goat hair fell from 28 (1929-1938) to 12 (1939-1942) masking the increase of 15 to 29 cases among cases related to wool. (57)

From 1935-1955, 117 cases of anthrax occurred (116 cutaneous) in Chester, PA. The great majority (104 of 116) were related to a local mill that uses goat hair for making liners of men's coats. Definite trauma to the skin was present in many cases; usually a minor scratch. Gold found the US provided "totally inadequate federal regulations." Studies of the mill in 1955 showed anthrax spores from air samples, dust collected from machinery, walls, floors, clothing.

The highest yearly incidence occurred in 1940 and 1941, respectively. (12,15) Incidence was highest during WWII when the regulations at the port of exit were relaxed. The source of infection was typically linked to Asia (China, Pakistan, India) or Morocco. (58)

Two major outbreaks have been reported in the United States wool industry. In 1917, Dr. Walter H. Brown reported 25 cases of human anthrax to the Connecticut State Department of Health in four months, constituting 'the largest single outbreak of the disease ever recorded in Massachusetts history.' (59) Three cases were fatal, twenty-two recovered. Through epidemiological investigation, it was shown that hides were imported from regions of China where anthrax was endemic. Brown demonstrated that the hides were shipped to the involved tanneries, handled by the workers who came down with anthrax, and that no other tanneries reported anthrax cases during the outbreak period.

Brachman presented the 1957 NH outbreak as the most deadly inhalation anthrax outbreak of the 20th century. Five inhalation and four cutaneous cases occurred. (60) The Brachman study provided many interesting insights. He highlighted the importance of the industrial process of handling wool in increasing the risk to workers of exposure to infected materials. The process involves: Step 1. Picking room where wool is scoured and blended. Step 2. Carding room where wool is combed. Step 3. Spinning. Step 4. Weaving Step 5. Finishing. Picking was found to be the dirtiest job but not the dustiest. Also, that particular factory was well ventilated in the Picking room. Carding and combing were the dustiest areas with no windows. Brachman found four of the five inhalation anthrax cases occurred with those workers in the carding and combing department. Brachman eventually attributed the outbreak to the dustiness in the card and combing room.

Outbreaks of anthrax in human populations also have been noted to involve modes of transmission other than agricultural or industrial involvement. Bales details 5 CDC investigations of anthrax outbreaks due to these "Other" exposures. (36) For example, shaving brushes were known to be an early non industrial cause of anthrax. (61,62) In 1918, cases of anthrax occurred among troops in various US military training camps. Fourteen of nineteen cases were proven to have originated from infected shaving brushes in general issue toiletry kits. In each case, a new brush was used just before a malignant pustule appeared and that virulent anthrax was found on the brush. Similar brushes obtained from involved wholesalers were shown to be contaminated with anthrax. Brushes with mixed horse hair from China and Siberia were implicated. Laboratories, gelatin factories, bone meal, plumbing supplies such as goat hair insulation have all been implicated in the most recent cases of anthrax. Craftsmen have also been infected given their use of raw materials, circumventing of US importation regulations, and lack of vaccination. In 1974, Haitian crafts were implicated in a FL case investigation. (36) In 1976, thread from Pakistan lead to infection. (152) In 2006 two unrelated cases of inhalation anthrax occurred in makers of drums in New York City and rural Scotland involving West African goat hides (63,64)

A recent anthrax case in Pennsylvania serves as a good case study for contemporary occupational inhalation anthrax. **Table 5** provides a timeline for the case with references. Vado Diomande, a member of an African dance troupe, collapsed after performance at local college. Diomande presented to a local hospital and reported a two to three day history of dry cough, shortness of breath, profuse diaphoresis, and general malaise. (65,66) Anthrax was added to the patient's differential diagnosis once his exposure to raw African goat hides became known. (67,68,69) After three days of clinical evaluation and examination of blood culture results, the

CDC was notified and a specimen was transferred to the Laboratory Response Network laboratories. (69,70,71) In the meantime, FBI, police, CDC investigators, and local law enforcement and first responders amassed at the patients home and work areas around the New York City metropolitan area. (72,73,74) It was established through environmental investigation of the patients workshop in Brooklyn, NY that the exposure was occupational and not due to bioterrorism. (75,76)

The social consequences of this anthrax case were tremendous. Major media coverage began immediately after the diagnosis of inhalation anthrax was confirmed. The first hours of media reporting brought anxiety among those in the PA and NY region, concerned over the possible threat of terrorism. Public health messaging stressed the occupational exposure and stressed no known link to terrorism was evident. Seven contacts of the patient were put on prophylaxis. National and regional media outlets provided around the clock coverage for about 7 days. Vado Diomande, the anthrax patient, became a local celebrity around New York City as his resilience and good nature during the difficult hospitalization were broadcast. (77,78)

Table 5. Timeline for Inhalation Anthrax Case. New York, NY. 2006

12/21/2005 - Brooklyn resident bought raw cow and goat hides in Africa over Christmas holiday for drum making. (65, 66)
02/12/2006 - Man worked on last of the hides. Soaking, stretching, drying hides and then scraping. The hair was removed mechanically using a razor in a small, poorly ventilated workspace.
02/15/2006 - Man cleans up workshop in Brooklyn warehouse.
02/16/2006 - Man collapses after performance at local college. Presents to hospital and reports two to three day history of dry cough, shortness of breath, profuse diaphoresis, and general malaise. The patient appeared ill and exhibited mild respiratory distress. Posterior-anterior and lateral chest radiographs revealed cardiomegaly, a left upper-lobe opacity, and a small lower-lobe opacity. Bilateral infiltrates and pleural effusions were noted. Blood cultures were performed.
02/17/2006 - Patient transferred to tertiary care center due to worsening respiratory distress. All four blood culture bottles grew gram positive rods. Inhalation anthrax was believed to be a significant possibility at the time of transfer on the basis of finding of gram positive rods in the initial blood cultures. Chest CT revealed a large amount of mediastinal fluid accumulation extending from the great vessels to the heart. Mediastinal lymphadenopathy was not present.
02/20/2006 - Test began to indicate the possible presence of anthrax.
02/21/2006 - 1. CDC notified after isolate initially evaluated at hospital. 2. LRN and PCR positive from blood culture isolate positive for *Bacillus anthracis*. 3. PA DOH tests positive for *Bacillus anthracis*. 4. PA DOH public health investigation began after laboratory tests detected anthrax bacteria. NYCDOHMH notified of case of inhalation anthrax in a resident of Manhattan drum maker. 5. CDC arranges transport of isolate to Atlanta for further testing.
02/22/2006 - 1. First media reports of case. CNN, CDC, NYCDOH, PADOH all issue press releases. Tom Skinner, spokesman for the CDC and Dr. Lisa Rotz, medical epidemiologist hold press conference and conference call. 2. Gamma phage lysis positive for *Bacillus anthracis*. 3. PA DOH reports no reason to believe the case is linked to an intentional release. CDC and FBI assisting on investigation. 4. CNN reports positive test for anthrax, links case to African drums. 5. CDC dispatches Environmental and Epi-investigation team to New York City to assist with environmental investigation. Hypothesis is that animal hides were carrying spores and preparation for drum making aerosolized them. (67,68,69,70,71)
02/22/2006, 15:58 - CDC reports blood culture isolate positive for *Bacillus anthracis*.
02/22/2006, 17:00 - Man's apartment was sealed by response team including federal agents, police officers, fire fighters, and other city workers. Some investigators carried radiation detectors and others wore protective suits to test for evidence of anthrax production. (72,73)
02/24/2006, 16:08 - Laboratory testing identified *Bacillus anthracis*. Seven persons on post exposure prophylaxis. (74,75,76,77,78)

Overall, the frequency of anthrax infection in human populations has declined to isolated and sporadic agricultural cases, imported materials, and labs. Several public health measures

greatly affected the incidence of anthrax in the last 50 years. In 1951, Wright successfully demonstrated the safety and effectiveness of a human anthrax vaccine by injecting 600 personnel at Fort Dietrich, Maryland. (79) In 1962, Brachman conducted a field study of the vaccine on leather workers at a Philadelphia tannery, a susceptible industrial population known to be chronically exposed to anthrax. The vaccine was shown to have 92.5% effectiveness with only 2.8% of workers developing local edema. (80) A 2003 review by Grabenstein summarizes recent progress in the field of anthrax vaccines. (79)

Today, Anthrax Vaccine Adsorbed (AVA) is the only licensed human anthrax vaccine in the United States. Routine vaccination with AVA is indicated for workers involved in the production of large quantities or concentrations of B. anthracis cultures and in personnel whose activities have a high potential for aerosol production. Laboratory workers using standard Biosafety Level 2 practices in the routine processing of clinical samples are not at increased risk for exposure to B. anthracis spores and should not receive the vaccine. Postexposure prophylaxis against *B. anthracis* with ciproflaxin is recommended following an aerosol exposure to *B. anthracis* spores. (81)

Federal regulations have also had a profound effect on materials imported into the US. The Code of Federal Regulations clearly outlines safety and sanitation measures directly related to materials key in the textile industry in "Title 9: Animals and Animal Products. Sanitary Control of Animal Byproducts (except casings), and Hay and Straw, Offered for Entry into the United States". (82) Materials covered by the regulations include bone meal, hides, skins, wool, hair, bristles, glue stock, bones, horns, animal manure, hay, straw.

3.5 ANTHRAX AS BIOLOGICAL WEAPON

In the past 50 years, public health concern of anthrax exposures has shifted from "other" exposures to the deliberate use of anthrax as a biological agent. In 1979, Soviet health officials from the Russian city of Sverdlovsk reported a very large outbreak of anthrax with an implausible explanation of tainted beef. Most likely, the Soviets were attempting to conceal a violation of the Biological and Toxin Weapons Convention which strictly forbade the manufacture or development of weaponized anthrax as of 1972. (83) The reporting of the NY Times repeatedly cast a shadow of doubt on the plausibility of over a thousand Soviet citizens dying from 'tainted beef.' As Soviet officials changed their story, US public health officials put forward the possibility of a release of weaponized anthrax spores. (84, 85, 86, 87, 88, 89, 90, 91,92) Editors of scientific journals discussed the possibility. (93)

Later, CDC investigators, led by Matthew Meselson were given access to Sverdlovsk for an epidemiologic investigation. Epidemiologic results supported an inhalation anthrax outbreak over the reported gastrointestinal outbreak. (94) Knowledge of the agent, exposure, route of infection of anthrax guided the investigators through an epidemiologic investigation. This was later published as a work of non-fiction. (95) Molecular epidemiologic studies later confirmed the strains of anthrax use by the Soviets for the biological weapons. (96)

Table 6. Anthrax as a Biological Threat

1972 - The U.S. and more than 100 nations sign the Biological and Toxin Weapons Convention, the world's first treaty banning an entire class of weapons. The treaty bars possession of deadly biological agents except for defensive research including anthrax. (83)
1979 - A rare outbreak of anthrax disease in the city of Sverdlovsk killed nearly 70 people. The Soviet government publicly blamed contaminated meat, but U.S. intelligence sources suspected the outbreak was linked to secret weapons work at a nearby army lab. (83,84,85,86,87,88,89,90,91)
1991 - After years of warfare with the U.S., Iraq possessed weaponized anthrax, botulinum toxin, and aflatoxin and had several other lethal agents in development. Inspectors from the U.N. Special Commission (UNSCOM) spent more than two years pursuing evidence of the program. The UNSCOM team found that Iraq's stockpile included Scud missiles loaded to deliver pathogens. From 1991-2002, U.S. Intelligence reports assert Iraq has maintained an active, covert Biological weapons program capability to convert quickly legitimate vaccine and biopesticide plants to biological warfare production. (97)
1991 - “Saddam Hussein regarded BW as an integral element of his arsenal of WMD weapons, and would have used it if the need arose.” (97)
1992 - U.S. team of epidemiologists led by Matthew Meselson visit Sverdlovsk, Russia. The team's investigation found evidence in the lungs of victims that many died from inhalation anthrax, likely caused by the accidental release of aerosolized anthrax spores from a military base. (94)
1995 - The religious sect Aum Shinrikyo released sarin gas in a Tokyo subway, killing 12 commuters and injuring thousands. The cult also had enlisted Ph.D. scientists to launch biological attacks including anthrax. Between 1993 and 1995, Aum Shinrikyo tried as many as 10 times to spray botulinum toxin and Sterne vaccine spores in downtown Tokyo. (100)
1998 - Nevada state police arrest Larry Wayne Harris and William Job Leavitt with eight flight bags of ‘military grade anthrax’ in the trunk of their Mercedes-Benz. Larry Wayne Harris and William Leavitt ‘conspire to possess’ weapons grade anthrax spores. (102)
1998 - FBI reports escalating terrorist threats of biological weapons. Rising from 37 in '96, 74 in '97, to 181 in '98. FBI reports “Threatened release of biological agents, such as anthrax or Bubonic plague, has become the most prevalent component of this disturbing trend.” (103)
2001 - In response to WTC Attacks on 9/11, CDC dispatched 45 EIS officers for drop in surveillance looking for “specified clinical syndromes to identify unusual disease manifestations or clusters”. (104)
2001 - 11 cases of inhalation anthrax and 11 cases of cutaneous anthrax. Increased awareness of the potential for a large-scale attack.
2002 - ‘Anthrax hoaxes’ continue to disrupt daily operations at government buildings. In August 2002, U.S. District Judge Mary Lou Robinson received a letter containing a white powder with a threateningly worded letter. An entire Texas federal building was closed for the rest of the day and into the following day. (98)
2004 - Roger V. Evans mailed a letter to the federal courthouse in Pensacola, Fl, addressed to the Clerk of the U.S. District Court. The letter, entitled “Affidavit in Support of Anthrax Scare” referenced anthrax three times and contained a white powder, later determined to be harmless. Several employees were isolated for up to ten hours and then taken to the local hospital to draw blood for testing. (99)

A third epoch in the last hundred years of anthrax centers on the history of bioterrorism using anthrax spores. Anthrax as a perceived biological threat is presented in **Table 6**. In the last ten years, terrorist groups have embraced anthrax as an agent for destruction or as a threat. In recent years, in spite of the international ban on biological weapons, the former Soviet Union was shown to maintain the capacity for manufacturing weapons grade anthrax aerosols. (100,101)

Domestically, the CIA has documented that threats of anthrax, both real and perceived, had reached an all time high in 1998 with almost one incident every three days. (103) "Anthrax Hoaxes" are known to cause chaos in federal buildings and medical clinics where abortions are performed due to the intensity of response by local authorities. (102,103)

The September 11th, 2001 destruction of the World Trade Centers in New York City heightened the United States public health officials' awareness to the possibility of a biological release of a weaponized agent. (104,105)

Bioterrorism-related anthrax became a reality in September, 2001. On approximately September 19th, a letter addressed to Jennifer Lopez containing a Star of David and a bluish powder arrived in the mailroom of American Media Inc. (AMI), publisher of celebrity periodicals Sun and National Enquirer, in St. Petersburg, FL. The letter is illustrated in **Figure 3**. (106,107) Ernesto Blanco, AMI mail supervisor, received and then delivered the mail. Several people handled the letter. Robert Stevens closely examined the letter and sniffed some of the powder. Both would be stricken with anthrax in a matter of one week. (19,108,109)

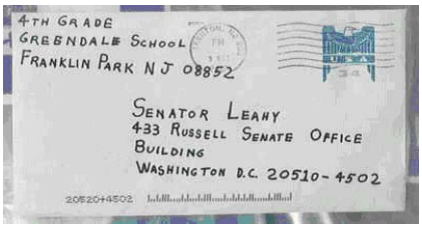


Figure 3. Anthrax Letter

Because human anthrax had become such an infrequent disease, very little was understood of the disease except by few public health scientists and veterinarians. Initial media reports treated the case as an isolated incident similar to craftsmen infections.

A typical inhalation anthrax exposure could not be initially identified for Robert Stevens, the apparent index case of anthrax. He did not work in a factory. He did not work with animal materials. Initial reports concentrated on several facts. Robert Stevens was an avid fisherman and outdoorsman. He had recently vacationed in North Carolina. Investigators searched his home, workplace, and over 50 places he had visited around his hometown of St. Petersburg, FL in the prior 20 days. It was at his workplace, a news media outlet, environmental samples tested positive. Once a mail handler in the same office fell ill investigators began to piece together the route of exposure.

Weaponized anthrax has a wider dispersion than industrial anthrax aerosolized in textile mills. It is designed at an optimum size for inhalation. Investigators also found implicated letters to be electrostatically charged to spread the spores during the process of opening. At least 4 letters were mailed from October, 2001 to November, 2001. An estimated 32,000 persons initiated antimicrobial prophylaxis. Completion of a 60-day course of antimicrobial prophylaxis was recommended for approximately 10,300 persons. (108)

This outbreak was a new and unique source of anthrax exposure. Over the course of US public health history, the epidemiology of anthrax has shifted from an infection primarily

associated with animals and animal products to an odorless, colorless powder capable of infecting many if place in an envelope and mailed. The ensuing media coverage placed today's anthrax threat from bioterrorism in context with what had previously been an agricultural or industrial disease. New methods of monitoring for anthrax must take into account that no obvious initial exposure may be known for a patient exhibiting signs of the disease. Excerpts of the early media reports follow below.

> "Case appears to be isolated."… "Sporadic cases of anthrax do occur in the United States, so a single case is not an indication of an outbreak. The last case of anthrax reported in the United States was earlier this year in Texas." … "The Florida State Health Department and a team from CDC are aggressively investigating the source of infection. They are reconstructing the patient's schedule for the last few weeks to attempt to determine the location where the patient may have been exposed. A team of CDC epidemiologists were sent to Florida to look for any indications of exposure to this disease. "… "They should not buy gas masks." HHS – Public Health Message Regarding Anthrax Case. (2) CDC – Public Health Message Regarding Anthrax Case (110)
>
> "Local health department stressed occupational exposures." FDOH – Health officials investigating isolated and non-contagious case of anthrax (111)
>
> "The investigation is looking into every aspect of this man's activity, as he was an avid outdoorsman." PBCHD – Anthrax confirmed in Lantana Resident (112)
>
> "Florida's first confirmed case of anthrax in 27 years surfaced Thursday in Palm Beach County, prompting an intense investigation by federal and state health officials and assurances that the isolated case had no link to last month's terrorist attacks." … "But he said a deliberate release of the germ by terrorists is one of several possibilities under investigation. 'We have that on the list', said Dr. Jeffrey P. Koplan, director of the Centers for Disease Control and Prevention in Atlanta."… "Yet federal Health and Human Services Secretary Tommy Thompson noted that Stevens, described as an avid outdoorsman, apparently drank from a stream while in North Carolina, a state known for hog farming and its associated waste." St. Petersburg Times – 'Terror or accidents?' – Anthrax – CDC, FBI Investigate Lantana Case (113)
>
> "The FBI is working with health officials in Florida and at the Centers for Disease Control and Prevention (CDC) to locate the source of the man's illness, but one spokesman said, 'There is absolutely no indication this is tied in any way to terrorism.'" CNN – Florida man suffering from Anthrax Dies (114)

4.0 CLINICAL CHARACTERISTICS OF INHALATION ANTHRAX

Inhalation anthrax exhibits a distinct clinical picture. This signature presentation makes surveillance possible for early signs and symptoms of the disease. Chapter 4 provides a clinical examination of anthrax to better understand the complex pathogenesis of the disease as well as a detailed review of case reports published in the literature.

4.1 PATHOGENESIS OF INHALATION ANTHRAX

How does anthrax create such havoc in the body of those affected? The following section outlines the basic patho-physiology associated with anthrax and the major steps in the early phase of inhalation anthrax infection.

Anthrax first gains entry to the host through inhalation of spores. The spores then germinate and multiply locally within the lungs. The germinated bacteria are then engulfed by macrophages and transported to the lymphatic system. (115) Anthrax bacteria continue to multiply and produces toxin within the macrophage while traveling to the lymph nodes. *B. anthracis* next escapes from the macrophage, killing it in the process. (116,117) The killing of the macrophage prevents the secretion of proteins, chemokines and cytokines, which can alert the immune system to the presence of the anthrax pathogen. Thus, once freed of the macrophage, the capsule of the *B. anthracis* inhibits phagocytosis by macrophages. (118,119) When bacteria reach the regional lymph nodes, they multiply extracellularly to very high concentrations within the blood. In inhalation anthrax, the multiplying bacteria accelerate the release of toxins which

affects the endothelial cells of the vascular system leading to breakdown of blood vessels, hemorrhage, and massive pulmonary edema.

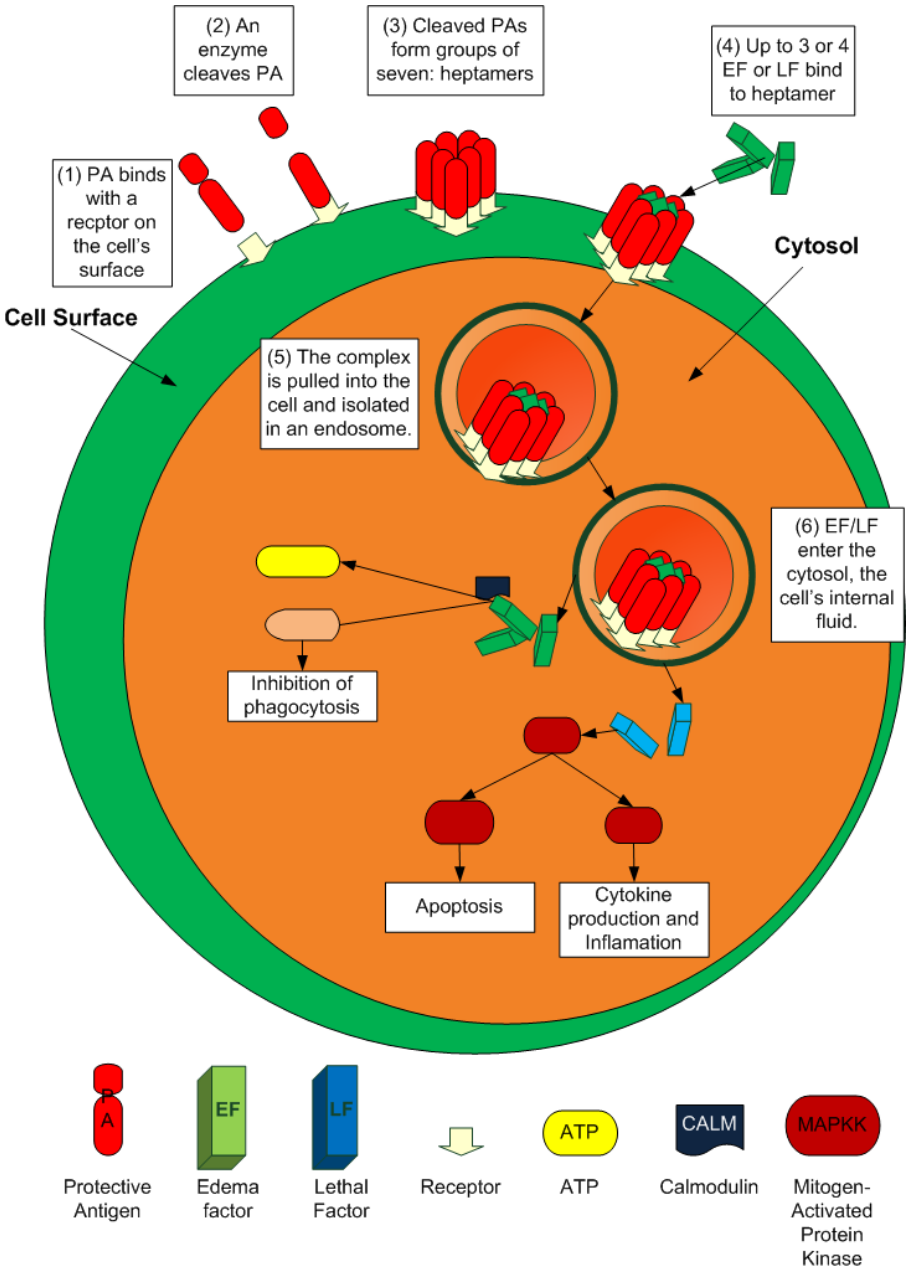


Figure 4. Anthrax Toxin Action

Toxin production is the key to anthrax pathogenesis. To be virulent, *B. anthracis* must be encapsulated and produce a three component toxin consisting of Edema Factor (EF), Lethal Factor (LF), and Protective Antigen (PA). EF and LF are not biologically active on their own. However, EF and PA couple to produce Edema Toxin (ET); and then LF and PA combine to make Lethal Toxin (LT). Both toxins exhibit unique properties. (120,121,122) **Figure 4** illustrates the toxin action of *B. anthracis*. This is described below in detail.

Generally when inhaled, the anthrax spore is surrounded by alveolar macrophages as a normal response by the immune system to a pathogen. Protective antigen (PA) then attaches to a receptor on the surface of the macrophage. (123) A portion of the PA is cleaved off by a cellular protease (Furin), an enzyme that breaks down proteins, exposing a binding site for LF or EF. (124) PAs form into groups of 7 called heptameters and bind up to three copies of EF or LF. The heptameter complex (PA+LF or PA+EF) then inserts into the cell membrane. (125,126,127,128) Through endocytosis, the heptameter complex enters the endosome, a membrane bound compartment inside eukaryotic cells such as macrophages. The heptameter complex subsequently responds to a lower pH within the endosome and forms a channel in order to release the toxins into the cytosol. Lethal toxin stimulates macrophages to release proteins involved in inflammation, interleukin-1β and tumor necrosis factor α, which are partly responsible for systemic shock. (129,130) Lethal toxin also suppresses the inflammatory response in the macrophage and switches the signal for activating an immune response to a trigger for cell death, apoptosis. (131,132,133,134) Edema toxin upsets the balance of an important relay between the intracellular signal messenger cAMP and ATP which disrupts the water homeostasis within the cell leading to the accumulation of fluid beneath the skin or within

organs of the body such as the lungs. (135,136) Edema toxin also inhibits phagocytosis within the cytosol by an unknown mechanism. (137)

4.2 CLINICAL FEATURES

The major clinical findings of inhalation anthrax (IA) are outlined below. IA has a clinical pattern marked by two phases; a mild initial phase followed by an acute and severe fulminate phase. The CDC describes the two stages of inhalation anthrax as "a brief prodrome resembling a mild viral respiratory, followed by the fulminate stage which shows development of hypoxia and dyspnea, with radiographic evidence of mediastinal widening". (138) Because the initial stages of anthrax resemble those of other illnesses, it is common for anthrax to go unrecognized until the later, more serious clinical events show themselves. Current research efforts seek to identify mechanisms to identify anthrax in its earlier, mild stage.

After inhalation of anthrax spores, the expression of symptoms begins after an incubation period of 1–6 days. Common symptoms of IA begin with fever, chills, drenching sweats, profound fatigue, minimally productive cough, nausea or vomiting, and chest discomfort. (139) Dixon also notes that myalgias, malaise, and a condition resembling an upper respiratory tract infection can also be expressed. (116)

The disease progresses to the fulminate phase within 2–3 days after the initial symptoms. Some individuals show a period of brief recovery from the initial symptoms, before deteriorating in the fulminate phase. Fulminate stage symptoms will most likely lead to hospitalization within 24 hours. (115) The fulminate phase is characterized by high fever, acute dyspnea, diaphoresis and cyanosis. Stridor, a high pitched breathing sound, is present in some patients because of

extrinsic obstruction of the trachea by enlarged lymph nodes, mediastinal widening, and subcutaneous edema of the chest and neck. At this point, the patient is at risk for progressing rapidly to shock, hypothermia, and death. (140)

Respiratory failure is a key finding of inhalation anthrax. Once patients have passed the prodromal phase of the disease, patients often complain of an increasing inability to breathe. Acute respiratory failure was acknowledged in all 12 cases of anthrax documented in the last 30 years.

Mediastinal widening is also a key finding of inhalation anthrax. Mediastinal widening is identified through radiological evidence. Because this anatomy is fairly obscure to most researchers, a brief overview is provided here. The mediastinum is the extra-pleural space within the thorax, lying between the lungs. It is bounded by the sternum anteriorly, the paravertebral regions posteriorly, the thoracic inlet superiorly, and the diaphragm inferiorly. (141) A lateral chest radiograph divides the mediastinum into 3 parts. The anterior mediastinum boundary line projects from the diaphragm and along the back of the heart and in front of the trachea to the neck. The posterior mediastinum is behind another vertical boundary line that connects a point on each of the thoracic vertebrae one centimeter behind its anterior margin. In between those two boundary lines lies the middle mediastinum. Using this definition, the anterior mediastinum contains the thymus, ascending aorta, heart, and pericardium. The middle mediastinum contains the trachea, esophagus, hili and hilar lymph nodes, aortic arch, and numerous other lymph nodes and nerves. The posterior mediastinum contains a portion of the descending aorta and numerous nerves, including part of the lymphatic chain. (141)

Mediastinal widening or hilar, peritracheal, or peribronchial lymphadenopathy from inhalation anthrax is well-documented in historical domestic cases. Suffin noted enlargement of

the left hilus in a craftsman exposed to contaminated yarn from Pakistan. (152) Laforce observed a paratracheal mass in a 46 year old male with an occupational exposure to anthrax. (52) Brachman commented on two cases – a 28 year old African American man with mediastinal widening on chest film and a 50 year old housewife whose autopsy revealed pathologic findings of hemorrhagic mediastinitis. (151) In necropsies from three of five cases of inhalation anthrax from a New Hampshire textile mill, Albrink reports numerous enlarged mediastinal lymph nodes, mediastinal lymph nodes that were "anthracotic discrete, and edematous," and enlarged tracheobronchial lymph nodes. (142)

Abramova has written extensively on the large epidemic of anthrax that occurred in Sverdlovsk, Russia in 1979 and resulted in the deaths of many persons. (143) A series of 42 necropsies consistently revealed pathologic necrosis of the thoracic lymph nodes in the lymphatic drainage of the lungs and hemorrhagic mediastinitis. Other pathological reviews of anthrax which document mediastinitis have been published by Vessal and Grinberg. (153,144)

4.3 DIAGNOSIS OF ANTHRAX

If there is no reason to suspect it, early diagnosis of IA is difficult. (140) Without reason for increased suspicion, the early, non-specific clinical manifestation would be easy to misdiagnose. The advanced disease may be recognizable by characteristic chest radiograph abnormalities. (145) The chest CT is helpful in detecting hemorrhagic mediastinal lymph nodes, and edema, peribronchial thickening, and pleural effusions; findings commonly seen in IA. (139) Gram stain and cultures should be obtained on blood or cerebrospinal fluid (CSF) samples of

patients in whom anthrax is suspected. Sputum from patients seldom yields positive smears or cultures. (145)

Definitive diagnosis of anthrax requires laboratory confirmation. The CDC laboratory criteria for confirmation of anthrax are 1) isolation of *B. anthracis* from a clinical specimen from a patient's affected tissue or site, with confirmation by direct fluorescent-antibody staining and gamma phage lysis; or 2) other supportive laboratory tests, including a) evidence of *B. anthracis* DNA by polymerase chain reaction (PCR) from specimens from a patient's affected tissue or site, b) demonstration of *B. anthracis* in a clinical specimen by immunohistochemical staining (IHC), or c) positive serologic testing by an investigational enzyme-linked immunosorbent assay (ELISA) that determined the concentration of serum immunoglobulin G (IgG) to the PA component of anthrax toxin; sera are considered reactive if antibody was neutralized by competitive inhibition. (146,147,148)

4.4 SUMMARY OF INHALATION ANTHRAX CASES

Recent studies have examined the signs of symptoms of anthrax in both historical naturally-occurring and recent bioterrorism related anthrax patients. Hupert et al. searched MEDLINE and Web of Science for adult human cases of anthrax between 1960 and 2000 using 'anthrax' and 'case report' and found a total of 11 reports on 17 cases. Kyriacou identified 36 naturally occurring cases that were identified from MEDLINE, textbooks, monographs, and Index Medicus. Cases ranged from the year 1880 through 1976. Each case was confirmed by epidemiological characteristics, autopsy findings, and bacterial verification. Kuenhert et al., as part of the 2001 CDC bioterrorism investigation team, reviewed and extracted data from

patient's medical records. A synthesis of clinical findings of the anthrax subjects reviewed by these investigators is presented in **Table 7.**

Kyriacou and Hupert both examined signs and symptoms of historical inhalation anthrax patients. While Hupert did not report numerator/denominator, the study did provide the percent positive for the finding among the cases. Both studies agreed that cough, chest pain, and dyspnea occurred with high frequency. Kyriacou also found that all subjects were reported to have chills, nausea, and vomiting. Among physical findings, both Hupert and Kyriacou found rales or rhonchi to be present in a high proportion of anthrax cases. Kyriacou also found a high temperature and tachypnea, rapid shallow breathing, for more than 8 minutes.

Kyriacou, Kuenhert, and Hupert all examined signs and symptoms among the recent bioterrorism related inhalation anthrax cases. All three studies found cough and dyspnea to be present in a high proportion of the cases. In addition, Kyriacou and Kuenhert both reported chills in a high proportion of the cases. Both Kuenhert and Hupert agreed that only 27% of cases had abdominal pain. Among physical findings for the anthrax cases, only Kyriacou presents a detailed breakdown of the results. Tachycardia was examined by all three studies, which was found to be present at least 80% of the time by Kuenhert and Hupert. Kyriacou and Hupert reported high temperature was found at least 60% of the time in the anthrax patients. Kyriacou also reports at least 90% of the anthrax cases were found to have tachypnea for more than 8 minutes.

Table 7. Signs and Symptoms of Inhalation Anthrax from the Literature

	Community-acquired pneumonia			Influenza-like illness			Influenza	Syndromic
	Kyriacou	Hupert	Kuenhert	Kyriacou	Hupert	Kuenhert	Hupert	Soulakis
Sign or symptom	**LR (95%CI)**	**LR (95%CI)**	**p-value**	**LR (95%CI)**	**LR (95%CI)**	**p-value**	**LR (95%CI)**	**LR (95%CI)**
Abdominal pain	.	.	0.71	.	.	NA	.	3.0(0.56,16.19)
Altered mental status	115(15.99-827.11)	HIGH	.	NA	HIGH	.	HIGH	8.2(1.8,36.5)
Chest pain	1.5(1.18-1.91)	1.3(0.9-1.8)	0.04	1.55(1.19-2.02)	2.6(1.9-3.7)	NA	1.7(1.2-2.5)	2.9(1.3, 6.1)
Chills	1.22(1.07-1.41)	0.9(0.7-1.1)	0.21	1.93(1.56-2.40)	0.9(0.7-1.1)	NA	0.8(0.7-1.0)	.
Cough	1.05(0.95-1.15)	0.9(0.7-1.1)	0.47	0.97(0.89-1.05)	1(0.8-1.2)	1	0.9(0.7-1.0)	3.3(1.9, 5.7)
Diarrhea	.	.	0.7	.	.	NA	.	.
Dyspnea	1.63(1.39-1.92)	1(0.8-1.4)	1	2.77(2.16-3.54)	8.6(5.8-12.8)	NA	5.3(3.7-7.4)	1.3(0.9,1.9)
Fatigue	.	.	NA	.	.	1	.	8.7(2.8, 27.4)
Fever	1.1(0.95-1.27)	.	.	1.76(1.45-2.14)	.	.	.	2.9(1.6, 5.3)
Headache	.	0.5(0.3-0.9)	0.76	.	0.4(0.3-0.7)	0.002	0.4(0.2-0.6)	16.4(2.1, 125.6)
Myalgias	.	.	0.21	.	.	0.01	.	26.2(3.7, 187.0)
Nausea	2.8(2.16-3.63)	.	.	5.75(3.75-8.82)	.	.	.	4.9(2.2, 10.7)
Vomiting	4.73(3.33-6.73)	.	.	9.7(5.46-17.22)	.	.	.	.
Nausea or vomiting	.	1.6(1.1-2.3)	0.002	.	5.1(3.4-7.5)	NA	5.1(3.0-8.5)	.
Rhinorrhea	.	NA	0.76	.	0.2(0.1-0.5)	0.0002	0.2(0.1-0.5)	
Sore throat	.	NA	1	.	0.2(0.1-0.5)	0.0001	0.2(0.1-0.4)	6.7(0.7, 67.4)
Sweats	13.2(6.38-27.33)	.	.	14.69(6.42-33.61)	.	.	.	7.6(2.4, 24.7)
Physical findings	.	.	.	.	.	.	.	
Abnormal lung exam	.	NA	.	.	6.6(5.0-8.7)	.	8.1(5.3-12.5)	.
DBP<75	1.38(0.88-2.17)	.	.	1.79(1.12-2.85)	.	.	.	.
SBP <130	1.76(1.24-2.51)	.	.	1.6(1.13-2.27)	.	.	.	.
Pale or cyanotic skin	70.82(9.6-520.8)	.	.	NA	.	.	.	.
Pulse oximetry<96%	2.17(1.30-3.61)	.	.	4.89(2.66-8.99)	.	.	.	.
Rales	1.25(1.11-2.08)	.	.	13.52(6.55-27.88)	.	.	.	.
Rhonchi	1.3(0.67-2.53)	.	.	1.5(0.76-2.96)	.	.	.	.
Rales or rhonchi	1.43(1.14-1.78)	.	.	4.19(2.94-5.99)	.	.	.	.
Tachycardia	1.51(0.27-2.06)	.	0.04	5.14(2.99-8.86)	.	0.0001	.	.
Tachypnoea > 18/min	1.09(1.00-1.20)	.	.	1.28(1.15-1.43)	.	.	.	.
High temperature	2.44(1.89-3.16)	0.7(0.5-1.0)	0.23	7.24(4.66-11.26)	1.2(0.9-1.7)	0.37	0.8(0.6-1.1)	.
Wheezes	0.75(0.27-2.06)	.	.	0.72(0.26-1.97)	.	.	.	.

4.5 INHALATION ANTHRAX CASE SERIES

Excluding the recent bioterrorism-related cases, eleven inhalation anthrax cases have been reported in the literature since 1960. An examination of the initial diagnostic impression, the time to onset of symptoms, major clinical findings, and eventual outcome of the case provides insight into the clinical anthrax presented in the literature.

Plotkin described an epidemic occurring within a ten week period at a goat hair processing plant in New Hampshire. (149) The clinical profile of the five presenting cases is detailed below:

Case 1: The diagnostic impression of the first case was influenza. The time from onset of symptoms to treatment was about five hours. The major symptoms were backache, headache, 102 degree fever, pulse 100, blood pressure 110/70. The case was fatal.

Case 2: The diagnostic impression of the second case was influenza. The time from onset of symptoms to treatment was about 1 day. The major symptoms were fever, cough, malaise, temp 104 degrees, slight rhinorrhea, non productive cough, wheezing, and profuse sweating. The case was fatal.

Case 3: The diagnostic impression was a severe flu, possibly bronchitis. The time from onset of symptoms to treatment was about 4 days. The major symptoms were 103 degree fever, cough, febrile, chest discomfort, and anorexia. The patient was found mumbling unintelligibly. The case was fatal.

Case 4: The diagnostic impression of the fourth case was possible cholecystitis. The patient was diagnosed with cardiac failure with superimposed pneumonia. The time from onset

of symptoms to treatment was about 3 days. The major symptoms were malaise, fatigue, mild pain in chest, cough, temperature of 99 degrees, pulse 92, respirations 24, and abdominal pain. Later, dyspnea, stridor, a productive cough, profuse diaphoresis, blood pressure 110/90, and bilateral rales developed. Radiography showed mediastinal enlargement, bilateral basal pleural effusions, and a middle lobe right lung effusion. The case was fatal.

Case 5: No diagnosis was assigned to the fifth case. The time from onset of symptoms to treatment was about 3 days. The major symptoms were fever (103 degrees), chills, cough, dyspnea, and profuse diaphoresis. An injection of 400,000 units of penicillin was prescribed. The patient was later hospitalized and developed a cough, slightly cyanotic, confusion, and rales. 800,000 units of procaine penicillin and 1 gm of dihydrostreptomycin were given every 12 hours. "Bacillus subtilis" was recovered. The identification was based on a gram stain of the nutrient broth culture. Since the technician believed the organism was a contaminant, the slide and culture were discarded without additional identification. (149)

La Force presented the clinical profile of one sporadic case of anthrax in a 46 year old man employed at a metal fabricator shop in New Hampshire in 1966. (150) Although an anthrax case never occurred at the metal shop, epidemiologic investigation revealed probable aerial spread of *B. anthracis* from a nearby goat processing plant located directly across a 60 foot alley. Plotkin described five known cases of inhalation anthrax occurring at this goat hair processing plant in 1957. (149)

Case 6: No diagnosis was assigned to the case. The patient's family went away on vacation and returned to find the patient in "a state". The patient had a history of diabetes and was found intoxicated and complaining of fatigue. 20 cc's of glucose through an IV, and insulin were prescribed. The major symptoms were confusion, lethargy, perspiration, unresponsiveness,

and shallow respirations. At the hospital rales and gurgling sounds developed. The disease was fatal.

Brachman described two cases of inhalation anthrax occurring in Philadelphia, PA. (151) Epidemiologic investigation failed to reveal anthrax exposure in either case. However, Case 1 worked at a furniture factory located 150 yards from a tannery known to have had anthrax case 12 years earlier. Case 1 caught the bus home across the street from the tannery on a daily basis. Environmental investigation revealed 10 of 147 swabs positive for *B. anthracis* at the tannery. Investigators presumed the factory as the source of infection. Case 2 lived 1 ½ blocks from the same tannery. Epidemiologists did not further investigate this case.

Case 7: The medical history of the first case included a 2 ½ year history of sarcoidosis with an episode 2 months prior. No diagnosis was assigned. The time from onset of symptoms to treatment was about 7 days. The major symptoms were dyspnea and frequent coughing, weight loss, 97.2 degrees temperature, 115 pulse, and respirations of 40. Later, chest pain, dyspnea, coughing pink sputum, acute distress, orthopnia, cyanosis, rales, and hemoptysis developed. The disease was fatal.

Case 8: The diagnostic impression of the second case was acute meningitis. The time from onset of symptoms to treatment was 2 days. The major symptoms were a "slight cold", vomiting, headache, and eventually coma. The disease was fatal.

Suffin presented the clinical profile of a 1976 case of inhalation anthrax in a California home craftsman. (152) The patient worked in his home as a self-employed artistic weaver and obtained his yarn from commercial sources. Investigation revealed the source of his infection as contaminated yarn imported from Pakistan.

Case 9: The diagnostic impression of the case was a hemorrhagic central nervous system process. The major symptoms were fever, sore throat, left-sided chest pain, headache, nausea, anorexia, tachycardia, decreased breath sounds, and unresponsiveness. The disease was fatal.

Vessal described the radiological and pathological findings of two out of five autopsy-proven cases of IA seen at Pahlavi University Medical Center in southern Iran. (153) Both cases stem from agricultural exposures. However, the authors do not elaborate on the source of infection.

Case 10: The first case was a 16 year old farm girl. She exhibited shortness of breath, painless swelling in her right axilla, and impending shock. The swelling increased and petechial hemorrhages appeared in the skin of the axilla. She was stuporous and in severe respiratory stridor. Radiology showed marked widening of the mediastinum with soft borders and a soft tissue swelling over the right chest wall. The differential diagnosis was cellulitis or blood dyscrasia. The disease was fatal.

Case 11: The second case was a 34 year old farmer. She exhibited a nonproductive cough, shortness of breath, hemoptysis, restlessness, clammy skin, deep labored respiration, tachypnea, cyanosis, shock. Radiology showed a marked widening of the mediastinum, massive consolidation, and middle zone bilateral pleural effusions, more prominent on the left. A lateral chest radiograph showed a dense shadow in the middle compartment of the mediastinum. A second radiographic series showed the same features plus infiltrates at both bases. Aspiration of a total of 1100 cc of serosanguinous fluid from both sides was performed. Complete listings of inhalational anthrax cases examined for this literature review are in **Appendix B.**

4.6 DISTINGUISHING EARLY STAGE ANTHRAX FROM SEASONAL INFLUENZA

Distinguishing early stage anthrax from seasonal influenza and influenza-like illness poses a challenge to health care providers. (154) Several clinical studies have attempted to identify clinical features useful for discriminating seasonal illnesses from bioterrorism related anthrax. The results are summarized in **Table 8**. (155,156,157,158) The most important components showing themselves from this work include a set of clinical features that are distinct from those seen in common viral respiratory tract infections such as acute respiratory distress and an abnormal chest x-ray. Screening protocols based on these features may improve identification of patients with possible inhalational anthrax in the setting of a large-scale anthrax attack.

Three important studies by Hupert, Kyriacou, and Kuenhert compared the presenting clinical characteristics of anthrax patients to the presenting clinical characteristics of patients with either community acquired pneumonia (CAP), influenza like illness (ILI), or influenza. All three authors reasoned that viral respiratory tract infections, such as influenza, respiratory syncytial virus (RSV), parainfluenza, and rhinoviruses or coronaviruses, are appropriate comparison conditions for their studies because of their prevalence and potential similarity to inhalational anthrax. All three authors also chose to compare anthrax cases to ambulatory patients with community-acquired pneumonia to highlight the difficulty of distinguishing these two conditions.

Table 8. Comparison of Findings of Three Clinical Studies

	Community-acquired pneumonia			Influenza-like illness			Influenza
	Kyriacou	Hupert	Kuenhert	Kyriacou	Hupert	Kuenhert	Hupert
Sign or symptom	**LR (95%CI)**	**LR (95%CI)**	**p-value**	**LR (95%CI)**	**LR (95%CI)**	**p-value**	**LR (95%CI)**
Abdominal pain	.	.	0.71	.	.	NA	.
Altered mental status	115(15.99-827.11)	HIGH	.	NA	HIGH	.	HIGH
Chest pain	1.5(1.18-1.91)	1.3(0.9-1.8)	0.04	1.55(1.19-2.02)	2.6(1.9-3.7)	NA	1.7(1.2-2.5)
Chills	1.22(1.07-1.41)	0.9(0.7-1.1)	0.21	1.93(1.56-2.40)	0.9(0.7-1.1)	NA	0.8(0.7-1.0)
Cough	1.05(0.95-1.15)	0.9(0.7-1.1)	0.47	0.97(0.89-1.05)	1(0.8-1.2)	1	0.9(0.7-1.0)
Diarrhea	.	.	0.7	.	.	NA	.
Dyspnea	1.63(1.39-1.92)	1(0.8-1.4)	1	2.77(2.16-3.54)	8.6(5.8-12.8)	NA	5.3(3.7-7.4)
Fatigue	.	.	NA	.	.	1	.
Fever	1.1(0.95-1.27)	.	.	1.76(1.45-2.14)	.	.	.
Headache	.	0.5(0.3-0.9)	0.76	.	0.4(0.3-0.7)	0.002	0.4(0.2-0.6)
Myalgias	.	.	0.21	.	.	0.01	.
Nausea	2.8(2.16-3.63)	.	.	5.75(3.75-8.82)	.	.	.
Vomiting	4.73(3.33-6.73)	.	.	9.7(5.46-17.22)	.	.	.
Nausea or vomiting	.	1.6(1.1-2.3)	0.002	.	5.1(3.4-7.5)	NA	5.1(3.0-8.5)
Rhinorrhea	.	NA	0.76	.	0.2(0.1-0.5)	0.0002	0.2(0.1-0.5)
Sore throat	.	NA	1	.	0.2(0.1-0.5)	0.0001	0.2(0.1-0.4)
Sweats	13.2(6.38-27.33)	.	.	14.69(6.42-33.61)	.	.	.
Physical findings	.	.	.	.	.	.	.
Abnormal lung exam	.	NA	.	.	6.6(5.0-8.7)	.	8.1(5.3-12.5)
DBP<75	1.38(0.88-2.17)	.	.	1.79(1.12-2.85)	.	.	.
SBP <130	1.76(1.24-2.51)	.	.	1.6(1.13-2.27)	.	.	.
Pale or cyanotic skin	70.82(9.63-520.79)	.	.	NA	.	.	.
Pulse oximetry<96%	2.17(1.30-3.61)	.	.	4.89(2.66-8.99)	.	.	.
Rales	1.25(1.11-2.08)	.	.	13.52(6.55-27.88)	.	.	.
Rhonchi	1.3(0.67-2.53)	.	.	1.5(0.76-2.96)	.	.	.
Rales or rhonchi	1.43(1.14-1.78)	.	.	4.19(2.94-5.99)	.	.	.
Tachycardia	1.51(0.27-2.06)	.	0.04	5.14(2.99-8.86)	.	0.0001	.
Tachypnoea > 18/min	1.09(1.00-1.20)	.	.	1.28(1.15-1.43)	.	.	.
High temperature	2.44(1.89-3.16)	0.7(0.5-1.0)	0.23	7.24(4.66-11.26)	1.2(0.9-1.7)	0.37	0.8(0.6-1.1)
Wheezes	0.75(0.27-2.06)	.	.	0.72(0.26-1.97)	.	.	.
Radiologic findings	.	.	.	.	.	.	.
Mediastinal widening	10.25(6.07-17.32)	.	.	23.11(8.65-61.74)	.	.	.
Mediastinal widening or pleural effusions	3.55(2.82-4.46)	.	.	22.6(9.59-53.24)	.	.	.
Laboratory study	.	.	.	.	.	.	.
High hematocrit or hemoglobin level	4.65(2.99-7.25)	.	NA	3.75(1.88-7.48)	.	0.004	.
Leucocytosis	1.26(0.98-1.62)	.	0.03	2.65(1.47-4.78)	.	0.04	.
Neutrophilia	.	.	0.71	.	.	0.06	.
High AST level	.	.	0.0004	.	.	<0.0001	.
High ALT level	.	.	0.0005	.	.	0.0008	.
Low sodium level	.	.	0.005	.	.	<0.0001	.
High BUN level	.	.	0.1	.	.	<0.0002	.
High creatinine level	.	.	NA	.	.	1	.
Low platelet count	.	.	NA	.	.	0.05	.
High bilirubin level	.	.	NA	.	.	0.009	.
Low potassium level	.	.	NA	.	.	0.21	.
Low albumin level	.	.	NA	.	.	<0.0001	.
Low calcium level	.	.	0.21	.	.	0.002	.

Each author differed in the method chosen for assembling a comparison population of CAP ILI, and influenza patients. Hupert searched MEDLINE for descriptive epidemiologic reports of presenting clinical features of laboratory-confirmed influenza and noninfluenza viral respiratory illnesses in ambulatory adults. Five published studies met the search criteria: a Phase II and Phase III clinical trial, a French influenza epidemic in 1995–1996 in which clinical and laboratory data were gathered by general practitioners, a 20-year surveillance study of RSV at a large academic medical center, a study of confirmed influenza cases presenting to the emergency department of a large metropolitan referral hospital, and a comparison of confirmed influenza cases to influenza-like illness cases from 14 Dutch general practice sites.

Kyriacou selected a comparison population of CAP patients seen in the ED at a teaching hospital affiliated with Northwestern University School of Medicine reasoning that CAP "is the disease that is most likely to be considered in patients with unrecognized cases of inhalational anthrax." An equal number of ILI patients were also selected at this site.

Kuenhert used data from patients with influenza or other causes of ILI from the combined patient population of 5 clinical trials designed to evaluate the effectiveness of zanamivir for the treatment of influenza. Kuenhert also collected data from a large study conducted at 34 sites in the United States and Canada from 1995 through 1999. All patients enrolled in the study were hospitalized because of acute CAP confirmed by chest radiography.

All three studies examined signs and symptoms of inhalation anthrax. Of the three studies examining fever as a discriminating factor for anthrax, only Kyriacou looked at subjective fever. Fever was found to be significantly different when anthrax patients were compared to ILI patients (PLR 1.76 [1.45, 2.14] but not CAP patients. Cough was examined by all three studies across CAP, ILI, and influenza patients. No significant differences were found. Hupert and

Kuenhert both looked at sore throat across CAP, ILI, and Influenza groups. Only Kuenhert found cough to be significantly high among anthrax patients when compared to ILI patients. Altered mental status, dyspnea, and nausea/vomiting are fulminant stage symptoms found in anthrax patients, and it is not surprising, then, that these features are seen proportionately more frequently in anthrax patients compared to ILI, CAP and influenza patients.

Physical findings were primarily examined by Kyriacou with only high temperature and tachycardia examined by Kuenhert and Hupert. Kyriacou found a significant difference in presenting body temperature when anthrax patients were compared to CAP and ILI groups but not to Influenza. Kuenhert and Hupert found no significant differences in body temperature between anthrax and the other patients. The most discriminating physical findings were tachycardia and a high hematocrit.

Only Kyriacou looked at radiological findings. He reported mediastinal widening as the most distinguishing feature when anthrax patients were compared to both CAP and ILI patients. (159)

Examination of the laboratory results of the inhalation anthrax cases revealed significantly high levels of hematocrit, leucocytosis, AST, ALT, and BUN in anthrax patients when compared to CAP patients. ILI patients significantly differed from anthrax patients across all lab values as CAP patients plus low platelet count, low albumin, and low calcium. The findings of Kyriacou and Kuenhert agreed on the significant difference in hematocrit and leucocyte levels among both CAP and ILI cases.

4.7 CASE STUDY - FLORIDA, 2001 IDENTIFYING ANTHRAX EARLY

Several opportunities exist to increase the timeliness of detecting anthrax using syndromic surveillance. **Table 9** on **page 55** is a timeline of the two recent cases of IA from the 2001 bioterrorism incident in the United States. This information was gathered from press releases, articles, books, and news broadcasts. The unfolding of the sequence of events beginning in September 2001 will serve as a detailed case study of the clinical recognition of bioterrorism related anthrax in the emergency department.

The timeline follows the simultaneous paths of Ernesto Blanco and Robert Stevens from the arrival of an anthrax letter to their AMI Inc. office to the development of flu-like illness to the eventual hospitalization and fulminate stage of the disease. One key feature of the timeline is the lack of knowledge of clinical staff and public health authorities of the existence of Blanco's case until three days after the admission of Stevens. The case study will highlight the missed opportunities to connect the cause of illness for Blanco and Stevens which ultimately decreased the timeliness of the detection of the outbreak of bioterrorism related anthrax in Florida.

Robert Stevens was a photo editor at the *Sun*, a popular weekly tabloid, since 1974. Stevens was primarily responsible for retouching celebrity photos. Ernesto Blanco was the mailroom clerk of American Media Inc., the parent company of the *Sun*. Blanco was a 73 year old retired carpenter. Blanco commuted by train and bus ninety minutes to Boca Raton, FL from his home in Miami. (162) His duties were to pick up the 3,000-5,000 pieces of mail AMI received daily from the post office. He sorted most mail on his own or with the aid of one other clerk, then wheeled the mail throughout the office on a cart. Although Stevens primarily worked with digital images, Blanco did deliver mail to Stevens on a daily basis as the *Sun* specialized in sensational journalism which elicited a large volume of submissions from amateur photographers

and readers. Sometime around September 5th, a letter addressed to Jennifer Lopez containing a Star of David and a bluish powder arrived in the Sun's mailroom in the American Media headquarters. Blanco received and then delivered the mail to Stevens, who in turn, closely examined the letter and sniffed some of the powder. (161)

Ernesto Blanco was the first of the two to seek outside medical help. He presented to the emergency department on Oct 1 with extreme respiratory difficulty eventually requiring a chest tube. A chest X-ray showed abnormal radiological findings, including upper and lower lobe infiltrates consistent with pneumonia and a small left pleural effusion. (160) The x-ray did not show mediastinal widening. A chest CT showed bilateral effusions and multilobar pulmonary consolidation but no significant mediastinal lymphadenopathy. Antibiotics were administered very early in the course of his care.

Stevens was admitted to the hospital the next day, Oct 2, with a condition closely resembling inhalation anthrax. His chest x-ray showed a prominent superior mediastinum and a possible small left pleural effusion. Six hours after admission, he had generalized seizures and was intubated for airway protection. Seven hours after admission, Stevens' attending physician observed a Gram positive bacillus through the microscope. He added Anthrax to his differential diagnosis immediately. By October 3rd, an investigation was launched by the Palm Beach Health Department based on the evidence of microbiological results supporting anthrax. The organism was nonmotile, non-hemolytic, and capsular. Testing was also positive for polysaccharide in the cell wall. The CDC would confirm the case the next day following the results of a positive gamma phage lysis test.

By October 4th, his third day in the hospital, Blanco's attending physicians were 'stymied':

> "…he had a typical presentation of a viral illness… We had x-rays consistent with bacterial pneumonia in someone who did not have a clinical picture of it. So you have to start working up all the atypical pathogens. Ernie had five or six dogs at home, so I thought maybe he has leptosporosis or something from the animals. It was a very bizarre presentation." (161)

The initial media coverage following the confirmation of Mr. Stevens as the first confirmed case of anthrax in 25 years stressed it was an isolated incident. Jeffery Koplan was quoted by the St. Petersburg times as saying "There's no need for people to fear they are at risk." By October 5th, 9 persons (5 cutaneous NY, 2 cutaneous NJ, 2 inhalational FL) had developed symptoms of inhalation or cutaneous anthrax due to direct or indirect exposure of tainted envelopes.

At 11:30 pm on October 5th, Blanco's attending physician would learn that another inhalation anthrax case had occurred in a hospital 75 miles away. His discovery was made by way of a phone call from a concerned colleague of Blanco's who remembered his sudden illness and subsequent hospitalization after CNN picked up the Stevens story after press releases from local, state, and national public health authorities. (161)

Fifteen days after admission, on October 15th, Blanco's case would be confirmed as positive for inhalation anthrax. This delay was caused by the requirements of the case definition. Subsequent testing revealed a positive PCR test for *Bacillus anthracis* in hemorrhagic pleural fluid and reactive serological tests. (162) Cell wall and capsular staining, PCR, or demonstration of the presence of antibodies to anthrax were nonculture tests. The case definition required a positive culture. A positive nonculture test and a clinically compatible case would only be considered a "suspected case" by the CDC. In the wake of unfolding events, the case definition was changed to two positive nonculture tests.

In the wake of the Florida cases, the CDC formally established a case definition to use for the 2001 bioterrorism-related anthrax investigations as follows: **Confirmed**: 1) Clinically compatible that is lab-confirmed by isolation of *B. anthracis* or 2) two supportive labs providing evidence of *B. anthracis*. **Suspected**: 1) A clinically compatible case of illness without isolation of *B. anthracis* and no alternative diagnosis, but with laboratory evidence of *B. anthracis* by one supportive test or 2) A clinically compatible case of anthrax epidemiologically linked to a confirmed environmental exposure, but without corroborative laboratory evidence of *B. anthracis* infection. In areas of heightened suspicion investigators conducted enhanced clinical case finding. Most sought to identify "clinically compatible" cases for further investigation.

Table 9. First Two Cases of Bioterrorism-Related Anthrax: Florida, 2001

Sept. 19th - Sometime within two weeks of this date, a letter addressed to Jennifer Lopez containing a Star of David and a bluish powder arrived in the Sun's mailroom in the American Media headquarters. Several people handled the letter. Stevens closely examines the letter and sniffs some of the powder. Blanco, the AMI mail supervisor, received and then delivered the mail.
Sept. 24th - Blanco has sudden onset of fatigue at work. Over the next three days experiences gradual progression of cough, lethargy, shortness of breath, and fever. He also begins sweating and having abdominal pains.
Sept. 27th - Stevens drives from Lantana, FL to Charlotte, N.C. for a family trip to visit daughter. Photo editor for tabloid leaves for North Carolina in good health.
Sept. 29th - Stevens experiences fatigue. Immediately on his arrival in North Carolina, the first symptoms of illness developed; these included muscle aches, nausea, and fever.
Sept. 29th - Blanco suffering nonproductive cough, fever, stuffy nose.
Sept. 30th - Stevens shivering and shaking, face red, severe weakness.
Oct. 1st - Stevens returned to his home from North Carolina early due to illness.. He spent most of the day in bed. Soaked with perspiration, nausea, temperature of 101 F. Worsening cough and headache.
Oct. 1st - Blanco admitted to Miami Cedars Medical Center. [65 miles from JFK in Atlantis]. Blanco was given the initial diagnosis of pneumonia. He was experiencing delirium and had difficulty breathing. Tests for Legionnaires' disease and hantavirus were negative. Physical exam pointed to pneumonia: wheezing sounds in lungs, diffuse consolidation on chest radiograph, and pulmonary infiltrates. Chest CT infiltrates consistent with pneumonia. Recurring pleural effusions required a chest tube. Arterial blood gas values showed hypoxia.
Oct. 2nd - Blanco's chest X-ray consistent with pneumonia.
Oct. 2nd, 02:00 - Stevens was admitted to the John F. Kennedy Hospital emergency room in Atlantis, Florida. presenting with disorientation, a high fever, vomiting, and inability to speak. Incoherent, delirious. Stevens was examined for meningitis by infectious-disease specialist Dr. Larry Bush. Bush found a high white blood cell count and rod-shaped bacilli; he soon was convinced Stevens had contracted anthrax. He then notified the Palm Beach County Health Department.
Oct. 2nd, 05:30 - Stevens seizures, intubated. Given spinal tap with a provisional diagnosis of meningitis. Treatment with intravenous cefotaxime and vancomycin was initiated for presumed bacterial meningitis while the patient awaited lumbar puncture. The initial chest radiograph was interpreted as showing basilar infiltrates and a widened mediastinum.
Oct. 2nd, 08:30 - Stevens' CSF cloudy, Gram stain positive and contains bacilli.
Oct. 2nd, 10:00 - Stevens' attending physician adds inhalation anthrax to differential diagnosis with high clinical suspicion.

Table 9. (Continued)

Oct. 2nd, 09:00 - Stevens sample of bacteria received by Integrated Regional Laboratories in Fort Lauderdale.
Oct. 2nd, 12:00 - Stevens laboratory results show bacteria to be nonmotile, nonhemolytic.
Oct. 2nd, 15:00 - PBCD Director Malecki is notified of Stevens' case. Florida state epidemiologist is notified.
Oct. 2nd, 18:00 - Stevens' specimens are sent to the Regional CDC Laboratory Response Network Laboratory in Jacksonville, Fl.
Oct. 3rd - Stevens' Jacksonville lab reports capsular test is positive for polysaccharide in the cell wall.
Oct. 3rd - Blanco's radiograph shows pleural effusions. His blood cultures are negative. Attending physician: "Patient had X-rays consistent with bacterial pneumonia but not the clinical picture of it." Blood cultures show no growth of infection.
Oct. 3rd - Formal investigation is opened by PBHD. 6 PBDOH staff investigate at hospital. Time spent reviewing Stevens medical charts and interviewing wife. In the evening, government investigators, including 12 investigators from the CDC, some from the Epidemic Intelligence Service, began their investigation into Stevens' movements of the last few days and potential sources of the anthrax. The hospital ships spinal fluid samples to state health officials and the CDC.
Oct. 4th, 08:15 - Gamma phage lysis positive. Stevens' diagnosis of anthrax is certain. The CDC confirmed the anthrax diagnosis. Federal officials announced that Stevens was admitted to a hospital on Tuesday with non-contagious pulmonary anthrax.
Oct. 4th, 11:00 - CDC investigators arrive on scene to investigate Stevens' case.
Oct. 4th - Media Reports: HHS - Public Health Message Regarding Anthrax Case. (163), CDC - Public Health Message Regarding Anthrax Case (110), FDOH - "Health officials investigating isolated and non-contagious case of anthrax"(111), PBCHD - "Anthrax confirmed in Lantana Resident." (112)
Oct. 5th, 06:00 - CDC investigators sweep through indoor and outdoor places Stevens had visited in last 60 days.
Oct. 5th, 23:30 - Blanco's attending physician notified of epidemiologic link to Stevens.
Oct. 5th, 12:00 - CDC investigators sweep Stevens' house.
Oct. 5th, 13:00 - Robert Stevens dies. Sweep of AMI.
Oct. 5th - Media reports: St. Petersburg Times - "Terror or accidents? – Anthrax – CDC, FBI Investigate Lantana Case." (113), CNN - "Florida man suffering from Anthrax Dies (114), FDOH - "Death of Mr. Robert Stevens." (164), New York Times - "Florida Man is Hospitalized with Pulmonary Anthrax." (165), CNN - "Gupta: Isolated anthrax case extremely rare" (166)
Oct. 6th - Steven's first round of samples collected are processed.
Oct. 6th - Media Reports: New York Times - "Florida man dies of Rare form of Anthrax." (167), St. Petersburg Times - "Anthrax Fatality is likely isolated." (168), "Single Anthrax Case Causes Few Ripples." (169)

Table 9. (Continued)

Oct. 7th - AMI samples collected from Stevens' keyboard and mailroom are positive.
Oct. 7th - Media Reports: CDC - Public Health Message Regarding Anthrax Case (170)
Oct. 8th - Media Reports: FDOH Continuing Investigation. (171) CNN – "Letter scrutinized as possible source." (172) St. Petersburg Times - "Tabloid workers tested for anthrax." (173)
Oct. 9th - Media Reports: St. Petersburg Times - "What is anthrax?" (174) "Monday's development." (175) "Officials are on Alert."(176) "Police, hospitals heighten vigilance." (177) New York Times. - "Puzzle of Anthrax in Florida." (178)
Oct. 11th - Media Reports: CDC - Public Health Message Regarding Anthrax Case. (179)
Oct. 12th - Media Reports: CDC - Public Health Message Regarding Anthrax Case. (180)
Oct. 15th - Blanco's diagnosis of inhalation anthrax officially confirmed. Blanco discharged October 23rd.
Oct. 16th - Media Reports: CDC – "Anthrax Investigation, FL and NY." (181)
Oct. 17th - Media Reports: CDC – "Update: Facts about anthrax testing and on-going investigations in Florida, Nevada, New York, and Washington, D.C." (182),CDC – "Update: Anthrax antibiotic treatments and CDC disease detective status." (183)
Oct. 18th - Media Reports: CDC – "Dr. Koplan, Director of CDC, answers important public health questions about anthrax." (184)
Oct. 19th - Media Reports: CDC – "Update: Investigation of anthrax associated with intentional exposure and interim public health guidelines." (185)

5.0 ANTHRAX SURVEILLANCE

5.1 TRADITIONAL ANTHRAX SURVEILLANCE

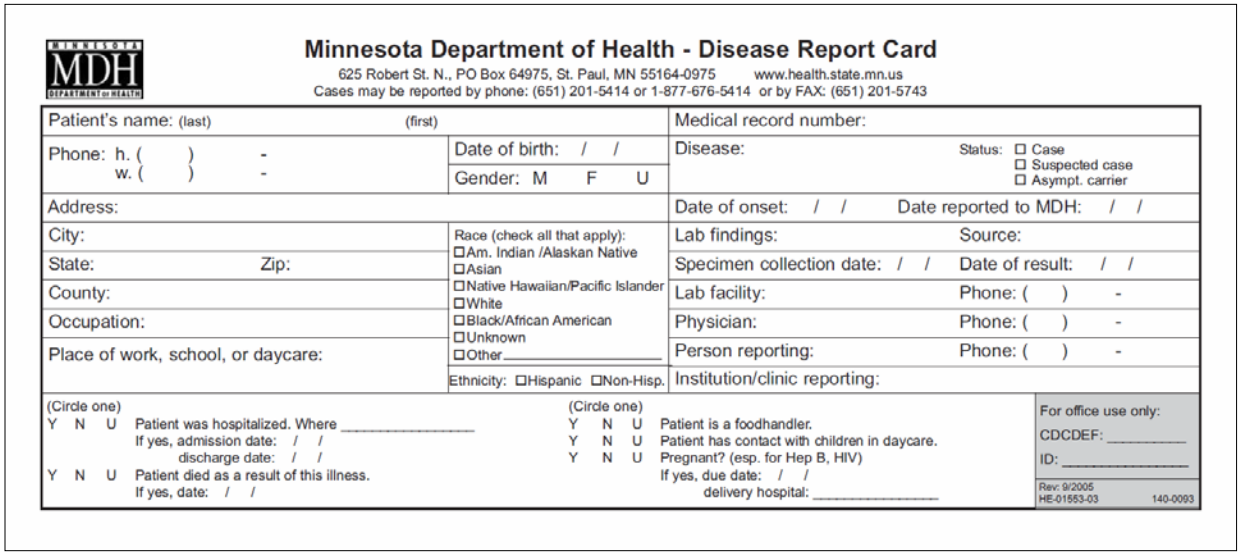
The previous chapters highlighted the current understanding of the public health impact and important characteristics of anthrax. The following chapter focuses on surveillance approaches that enable public health officials to identify outbreaks of anthrax.

Surveillance is defined in the Control of Communicable Diseases Manual as the "continued scrutiny of all aspects of occurrence and spread of a disease that are pertinent to effective control." (186) Operationally, surveillance involves a systematic and regular process by which data on disease are collected, evaluated, and reported. Examples of surveillance activities include the monitoring of infectious diseases through notifiable disease systems, identification of cancer and trauma characteristics through registries, regular field investigations of selected disease issues, and the isolation of infectious agents by laboratories. Surveillance involves not just the collection of information on disease with standard methods, but also the dissemination of this information. Public health authorities stress that summaries of surveillance information should be regularly distributed to all collaborating authorities and others with a need to know the results of the surveillance activities. (187)

Currently, anthrax is considered a Class 2 disease by the Control of Communicable Diseases Manual and is identified to public health authorities through the notifiable disease systems in their jurisdictions. (186) In this form of surveillance, clinicians, laboratories, and health care institutions should report a recognized case of anthrax by telephone to the public health authorities in their area as soon as possible. (186) As an example of typical public health

practice, anthrax reporting through a notifiable disease system is outlined below using the state of Minnesota guidelines.

In Minnesota, health care and laboratory personnel must report anthrax within 24 hours after the disease is reasonably expected to exist by telephone to the local health director. (188) The statutes also require a communicable disease report card or a report in an electronic format within seven days of the telephone report. **Figure 5** illustrates an example disease report card from the Minnesota Department of Health. (189) Isolation or other specific identification of *Bacillus anthracis* by a laboratory also requires a report by telephone within 24 hours. (190)



Minnesota Department of Health - Disease Report Card

625 Robert St. N., PO Box 64975, St. Paul, MN 55164-0975 www.health.state.mn.us
Cases may be reported by phone: (651) 201-5414 or 1-877-676-5414 or by FAX: (651) 201-5743

Patient's name: (last) (first)		Medical record number:
Phone: h. ( ) - w. ( ) -	Date of birth: / / Gender: M F U	Disease: Status: ☐ Case ☐ Suspected case ☐ Asympt. carrier
Address:		Date of onset: / / Date reported to MDH: / /
City:	Race (check all that apply): ☐Am. Indian /Alaskan Native ☐Asian ☐Native Hawaiian/Pacific Islander ☐White ☐Black/African American ☐Unknown ☐Other_____	Lab findings: Source:
State: Zip:		Specimen collection date: / / Date of result: / /
County:		Lab facility: Phone: ( ) -
Occupation:		Physician: Phone: ( ) -
Place of work, school, or daycare:		Person reporting: Phone: ( ) -
	Ethnicity: ☐Hispanic ☐Non-Hisp.	Institution/clinic reporting:

(Circle one)
Y N U Patient was hospitalized. Where _____
If yes, admission date: / /
discharge date: / /
Y N U Patient died as a result of this illness.
If yes, date: / /

(Circle one)
Y N U Patient is a foodhandler.
Y N U Patient has contact with children in daycare.
Y N U Pregnant? (esp. for Hep B, HIV)
If yes, due date: / /
delivery hospital: _____

For office use only:
CDCDEF: _____
ID: _____

Rev: 9/2005
HE-01553-03 140-0093

Figure 5. Minnesota Case Report Card

5.2 RATIONALE FOR SYNDROMIC SURVEILLANCE FOR INHALATION ANTHRAX

Although traditional surveillance serves as the foundation of public health practice by providing information for action for the control and prevention of naturally-occurring diseases, it may be inadequate for monitoring for bioterrorism related attacks. Syndromic surveillance monitors pre-diagnostic indicators of disease outbreaks. (191,192) By definition, syndromic surveillance precedes traditional laboratory-confirmed surveillance.

The response by top health officials immediately following the 2001 anthrax attacks clearly demonstrates the importance of syndromic data during an emerging outbreak. Health departments in Florida (193), North Carolina (194), New Jersey (195), Connecticut (196), and New York (208) all established continuous monitoring of Emergency Departments for clinical syndromes resembling fulminate-stage inhalation anthrax. In each case clinicians or epidemiologists posted at hospitals manually recorded demographic, clinical, and laboratory information on each patient meeting a syndromic case definition. Health departments made huge investments in ad hoc systems to collect and analyze the data and disseminate the results.

Proponents of syndromic surveillance find an advantage in the timeliness of the approach. In a resource-challenged environment like public health, some critics point out that the cost of the system is redundant if treating physicians report cases as they spot them. In the review of the literature "Syndromic Surveillance and Bioterrorism-related Epidemics", Beuhler et al. address the controversy of whether a syndromic surveillance approach is likely to detect an anthrax epidemic sooner than reporting by alert clinician. (197) Using the intentional anthrax release of 2001, they recount the major factors in the detection of a bioterrorism-related epidemic such as population characteristics, availability and use of health services, the nature of an attack,

epidemiologic features of individual diseases, surveillance methods, and the capacity of health departments to respond to alerts.

Briefly, their findings point out that most patients sought care during the mild phase of the illness at their primary care provider (as opposed to the Emergency Department) or were assigned diagnoses inconsistent with inhalation anthrax, that significant increases of febrile illness would most likely not been detected before patients were admitted for fulminate illness, and that most testing had grown a gram positive rod within 24 hours of admission. The authors conclude that an approach more sensitive and specific than syndromic surveillance for febrile illness but more rapid than growing a gram positive bacillus on culture would provide superior monitoring compared to the current state-of-the-art approach.

5.3 WHAT IS SYNDROMIC SURVEILLANCE?

The practice of syndromic surveillance grew out of a desire by public health authorities to prepare for large scale bioterrorism attacks. While some work in early detection of naturally occurring outbreaks does precede syndromic surveillance, most of the work focused on foodborne or waterborne pathogens. (198,199) Early published studies of syndromic surveillance first appeared in 1998 and accelerated in publication throughout much of the following decade until the present. (200) **Table 10** summarizes major works in syndromic surveillance. These papers, especially the early work, feature new approaches to conducting surveillance by evaluating computer systems which regularly collected administrative data from healthcare facilities in a semi-automated fashion and quickly processed it into a format suitable for epidemiologic analysis. This line of inquiry translated into surveillance systems for local health

departments which provide a daily snapshot of morbidity trends in the community. Most successful systems included surveillance for seasonal influenza, influenza like illness, or other respiratory illnesses. Local and local health departments in New York, Boston, Virginia, Indiana, Washington, and many others have run continuously for over a decade. The most often cited utility is tracking the onset and magnitude of influenza season. (201) Recent influenza tracking also included monitored pandemic H1N1 incidence in affected areas of New York City. (202)

The following chapter will outline the major components of syndromic surveillance including computer systems required to receive and process data, the variety of data sources commonly used, data types and coding schemes, and lastly analytical approaches commonly employed to identify outbreaks.

Table 10. Syndromic Surveillance Studies

Study (Year)	Region (Country)	System	Indicator	Data source	Data Type	Interval	Analysis Unit
Costaglia (1991)	National (France)	Sentiweb	Influenza-like Illness	Sentinelle	G.P. Report	Weekly	Number of visits/GP
Carrat (1998)	National (France)	Sentiweb	Influenza-like Illness	Sentinelle GPs	G.P. Report	Weekly	Number of visits
Toubiana (1998)	National (France)	Sentiweb	Influenza-like Illness	Sentinelle GPs	G.P. Report	Weekly	Number of visits
Tsui (2001)	Pittsburgh (US)	RODS	Influenza-like Illness	Emergency Departmer	ICD9 Code	Daily	Number of visits
Goldenberg (2002)	Pittsburgh (US)	RODS	Cough	OTC Sales	Medication	Daily	Number of purchases
Lazarus (2002)	Boston (US)	Harvard Vanguard Medical Assoc	L.R.T.I.	Ambulatory	ICD9 Code	Daily	Number of visits
Lewis (2002)	Washington, D.C. (US)	ESSENCE I	Fever	M.T.F.	ICD9 Code	Daily	Number of visits
Gesteland (2003)	Utah (US)	RODS	Constitutional	Emergency Departmer	Chief complaint	4 hours	Number of visits
Hogan (2003)	Multisite (US)	IN-PA-UT Collaboration	Respiratory	OTC Sales	Medication	Daily	Number of purchases
Mostashari (2003)	New York (US)	NYCDOHMH	Influenza-like Illness	E.M.S.	Call Types	Daily	Ratio of ILI to Other
Mostashari (2003)	New York (US)	NYCDOHMH	Influenza-like Illness	E.M.S.	Dispatches	Daily	Number of runs
Viboud (2003)	National (France)	Sentiweb	Influenza	Sentinelle	G.P. Report	Weekly	Number of visits
Reis (BMC) (2003)	Boston (US)	Children's Hospital	Respiratory	Emergency Departmer	Chief complaint	Daily	Number of visits
Heffernan (2004)	New York (US)	NYCDOHMH	Influenza-like Illness	Emergency Departmer	Chief complaint	Daily	Ratio of ILI to Other

Table 10 (Continued)

Study (Year)	Region (Country)	System	Indicator	Data source	Data Type	Interval	Analysis Unit
Kleinman (2004)	Boston (US)	Harvard Pilgrim Healthcare	L.R.T.I.	Ambulatory	ICD9 Code	Daily	Number of visits
Miller (2004)	Minnesota (US)	Health Partners Medical Group	Influenza-like Illnes	Ambulatory	ICD9 Code	Daily	Number of visits
Rogerson (2004)	Boston (US)	Harvard Vanguard Medical Assoc	L.R.T.I.	Ambulatory	ICD9 Code	Daily	Number of visits
Besculides (2005)	New York (US)	NYCDOHMH	Influenza	School	Absenteeism	Daily	Percent absent
Brillman (2005)	Albuquerue (US)	B-SAFER	Respiratory	Emergency Department	Chief complaint	Daily	Number of visits
Kulldorff (2005)	New York (US)	NYCDOHMH	Fever/Flu	Emergency Department	Chief complaint	Daily	Number of visits
Ritzwoller (2005)	Denver (US)	NBSSDP	Influenza-like Illnes	Ambulatory	ICD9 Code + M.T.	Daily	Number of visits
Wang (2005)	Boston (US)	Children's Hospital	Respiratory	Emergency Department	Chief complaint	Daily	Number of visits
Zhu (2005)	Florida (US)	University of South Florida	Respiratory	Hospital	Not Specified	Daily	Number of visits
Vergu (2006)	National (France)	Sentiweb	Influenza-like Illnes	OTC Sales	Medication	Weekly	Number of sales
Wong (2006)	National (Hong Kon	Hospital Authority	Influenza	Hospital	Hospitalizations	Weekly	Number of hospitalization
Burkom (2007)	Multisite (US)	Johns Hopkins	Respiratory	BioALIRT	Multiple	Daily	Number of visits
Cooper (2007)	National (England)	Health Protection Agency	Fever	NHS Direct	Nurse Calls	Weekly	Percent of calls
Haug (2007)	Air Force Bases (US	ESSENCE II	Influenza-like Illnes	M.T.F.	ICD9 Code	Daily	Number of visits
Jackson (2007)	Seattle (US)	King County	Influenza-like Illnes	Emergency Department	Chief complaint	Daily	Number of visits
Cooper (2008)	National (England)	Health Protection Agency	Fever	NHS Direct	Nurse Calls	Daily	Number of calls
Flamand (2008)	Bordeaux (France)	Sentiweb	Influenza-like Illnes	SOS Medicines	G.P. House Calls	Daily	Number of visits
Meyer (2008)	Gleneagles (Scotlanc	Health Protection Scotland	Multiple	Multiple	Multiple	Daily	Number of visits
Meyer (2008)	Gleneagles (Scotlanc	Health Protection Scotland	Multiple	Multiple	Multiple	Daily	Number of visits
Murphy (2008)	Multisite (US)	JPL	Respiratory	BioALIRT	Multiple	Daily	Number of visits
Cami (2009)	Houston (US)	RODS	Cough	OTC Sales	Medication	Weekly	Number of purchases
Najmi (2009)	NS (US)	JPL	Respiratory	M.T.F.	Multiple	Daily	Multiple
Tokars (2009)	National (US)	EARS	Influenza-like Illnes	Biosense	ICD9 Code	Daily	Number of visits

5.3.1 Computer systems

Figure 6. Typical Syndromic Surveillance Process

The process of syndromic surveillance is illustrated in **Figure 6.** (203) Syndromic surveillance systems typically operate in partnership with health departments, regional hospitals, healthcare delivery organizations, ambulatory care centers, and/or possibly universities or academic institutions. The Real-time Outbreak Detection System developed by the University of Pittsburgh and the New York City Department of Health and Mental Hygiene Syndromic Surveillance System are two good examples of currently operating systems. (204,205) These systems share similar characteristics such as the secondary use of automatically collected electronic data and short data collection intervals such as daily or hourly.

The computer systems that support syndromic surveillance can be a single computer system, integrated hospital computer systems, or integrated across hospitals in one health system. Syndromic surveillance is often continuously run 7 days a week or can be conducted on an ad hoc basis for major events such as the Winter Olympics in Utah (206), G8 meetings in Scotland (207), or in the wake of the 2001 World Trade Center attacks. (208) Personnel may run programs manually or review results from automated analysis. Personnel may need to retrieve missing data files and conduct quality assurance. (205) Investigations are typically conducted by local health authorities.

5.3.2 Data sources

Syndromic surveillance can leverage a wide variety of electronically available data sources such as over the counter drug sales (209,210,211,212), school absences (213), nurse hotline calls (214,215), emergency department chief complaints (216,217,218,219), emergency medical services dispatch types (220,221), measured temperatures (222), radiology reports (276), orders for chest x-rays (223,224), prescriptions, ICD9 codes (200,225,226,227), and progress notes (222). **Table 11** describes various data sources by type, setting, and phase of healthcare in which the data is generated.

Table 11. Sources of Syndromic Surveillance Data

Data source	Data type	Setting	Care phase
Medication sales	Drug category	Pre-clinical	Pre-diagnostic
School absences	Frequency	Pre-clinical	Pre-diagnostic
Nurse hotline call	Call type	Pre-clinical	Pre-diagnostic
Chief complaint	Text, brief	Clinical	Pre-diagnostic
EMS call	Run type	Clinical	Pre-diagnostic
Temperature	Vital sign	Clinical	Pre-diagnostic
Radiology Report	Text, narrative	Clinical	Pre-diagnostic
Chest X-ray	Procedure code	Clinical	Pre-diagnostic
Prescriptions	Drug category	Clinical	Diagnostic
Diagnosis code	ICD9 code	Clinical	Diagnostic
Progress Note	Text, narrative	Clinical	Diagnostic

Common data types include numeric, coded, brief text, or longer text narratives. Each data type requires varying degrees of sophistication to process. Data may be collected in many different settings to reflect any point of the disease process. However, it is desirable to collect data as close to the time of the onset of symptoms as possible.

Setting also effects representativeness of the data. *Pre-clinical settings* are individual-motivated such as staying home from school, buying an over the counter cough medication, or calling a nurse hotline. *Clinical settings* reflect healthcare encounters in ambulatory, ED, or inpatient settings where a patient interacts with the healthcare system such as stating a chief complaint to a clinician, or a clinician recording a patient vital sign, ordering an x-ray, prescribing a medication, diagnosing a patient, or documenting a progress note.

The care phase reflects progress through healthcare system. Pre-diagnostic is the assessment phase whereas diagnostic reflects the plan phase of the healthcare encounter where the physician has issued a diagnosis and considers treatment or referral options.

5.3.3 Data Types

Chief complaints are a common source of data given their wide availability and the pre-diagnostic care phase in which they are collected. However, chief complaints are often free text, requiring investigators to use keywords to identify patients with the syndrome of interest. (228) Natural language processing (NLP) techniques may also be used to code the data. Recent work by Travers describes the challenging characteristics of coding nurse's chief complaints including misspelling, punctuation, abbreviations, and spaces. (229,230) **Table 12** closely examines the respiratory syndrome from the NYC syndrome coding SAS macro. (231) Examination of the syndrome coding suggests that many patients coded as RESP will in fact not have the condition. This approach illustrates a highly sensitive strategy but at the cost of low specificity.

Table 12. NYC Syndromic Macro for SAS

Characteristic	Syntax
Respiratory conditions	%Macro Resp; *Respiratory; if cc=:**'COUGH'** or cc=:**'COUGHING'** or cc=:**'SOB'** or cc=:**'DifFICULTY BREATHING'** or cc=**'BREATHING PROBLEMS'** or cc=:**'SHorTNESS OF BREA'** or cc=:**'DifF BREA'** cc=**'URI'** or then *RESP*=1; else do; RESP=
Misspelling	index(cc,'**COUG**') + index(cc,'**COUH**') +
Shortness of breath	index(cc,'**S.O.B**') + index(cc,'**SOB**') + index(cc,'**S O B**') + index(cc,'**S O B**') + index(cc,'**S.OB**');
Difficulty breathing	index(cc,'**BREAT**') + index(cc,'**BEATH**') + index(cc,'**DIB**') + index(cc,'**D I B**') + index(cc,'**D.I.B**') + index(cc,'**BRATHING**') + index(cc,'**DifF BR**') + index(cc,'**DifF**, **BR**') +
Upper respiratory infection	index(cc,'**URI** ') + index(cc,'**URI**/') + index(cc,'**URI**;') + index(cc,'**U R I**') + index(cc,'**URI**,') + index(cc,'**U.R.I**') +
Other respiratory findings	index(cc,**'PNEUMON'**) + index(cc,**'GASP'**) + index(cc,**'PULMON'**) + index(cc,**'MONIA'**) + index(cc,**'INFILTR'**) + index(cc,**'CROUP'**) + index(cc,**'BRONCH'**) + index(cc,**'HYPOX'**) + index(cc,**'PLEUR'**) + index(cc,**'DYSPN'**) +
ICD9 codes in Chief Complaint	index(cc,**'786.2'**) + index(cc,**'786.0'**) + index(cc,'**480**') + index(cc,'**481**') + index(cc,**'482'**) + index(cc,**'483'**) + index(cc,**'465'**) + index(cc,**'466'**) + index(cc,**'484'**) + index(cc,**'485'**) + index(cc,**'486'**) +
Rule out certain combinations	if *RESP* GE 1
	or (index(cc,**'URTI'**) and (index(cc,**'URTIC'**) = 0 and index(cc,**'HURT'**) = 0))
	or (index(cc,**'CHEST'**) and index(cc,**'CONGEST'**))
	or (index(cc,**'RESP'**) and index(cc,**'RESPO'**) = 0)
	or (index(cc,**'CAUGHT'**) = 0 and index(cc,**'CAUGH'**)) or (index(cc,**'COLD'**) and index(cc,**'CHEST'**)) then *RESP*=1; else *RESP*=0;

Alcohol on breath	if *RESP*=1
	and (index(cc,**'ALCOHOL'**) or index(cc,**'ETOH'**))
	then *RESP*=0;
	END;
	%Mend;

The International Classification of Diseases, 9th edition (ICD9) encodes over 10,000 illnesses into numbered disease groups. (232) These codes can describe disease and conditions at

varying level of detail ranging from general organ system to precise anatomical location affected by the illness. Syndromic surveillance often leverages ICD9 data given it is readily available from most billing systems. The difficulty in using this coded data type is that investigators must determine which ICD9 codes correspond with the illness cluster to be monitored. ICD9 codes can be used for symptoms, diagnoses, or procedures. Diagnosis can stem from a variety of stages in the clinical workflow such as: working diagnosis, admitting diagnosis, discharge diagnosis. Multiple codes can be assigned per visit. ICD9 codes often include the disease process and organism responsible (e.g. ICD 481.00 - pneumococcal pneumonia) as well as non-specific syndromes such as ICD 079.99 - viral syndrome.

5.3.4 Analytical methods

Syndromic surveillance relies on informatics techniques to automate data collection and code exotic data types which are a relatively new practice in surveillance. However, traditional analytical techniques form the foundation of outbreak detection in many well-established syndromic surveillance systems. **Table 13** lists major syndromic surveillance studies from the published literature. While not exhaustive, a literature review taking into account the number of times a study was cited by syndromic surveillance practitioners was used to determine inclusion. Only studies with multiple citations were included. For instance, the 1963 Serfling study is not syndromic surveillance per se; however, it is one of the most highly cited surveillance papers given the popularity of the regression method among syndromic surveillance practitioners. Conversely, several excellent papers which were published this year were not included as their methods have not been widely adopted.

A general framework for syndromic surveillance is described in the sections that follow based on examination of these studies. Briefly, a typical analytical framework first establishes a baseline incidence of the monitored condition. A test statistic is then used to identify outbreaks by signaling significant departures of the observed from the expected rate of disease. The following section will review several popular approaches to establish the baseline and signal outbreaks.

Table 13. Syndromic Surveillance Analytical Approaches

Study (Year)	Analysis	Length of Baseline	Baseline	Anamoly
Serfling (1963)	Serfling regression	Not specified	Serfling regression	Threshold of 2 standard deviations increase for 2 weeks
Choi (1981)	Autoregressive integrated moving average	Not specified	Autoregressive integrated moving average	None
Costaglia (1991)	Serfling regression	Not specified	Serfling regression	Threshold of 2 standard deviations increase for 2 weeks
Carrat (1998)	Serfling regression	Not specified	Serfling regression	90% upper confidence interval
Toubiana (1998)	Serfling regression	Not specified	Serfling regression	Number of districts greater threshold
Tsui (2001)	Serfling regression	Not specified	Serfling regression	95% upper confidence interval
Goldenberg (2002)	Wavelet transform	Not specified	Wavelet transform	3 standard deviations
Lazarus (2002)	General linear mixed model	Not specified	General linear mixed model	p-value
Lewis (2002)	Autoregressive integrated moving average	Not specified	Autoregressive integrated moving average	95% upper confidence interval
Hogan (2003)	Exponential weighted moving average	28 day baseline with 2 day buffer	Not specifed	Exponential weighted moving average
Mostashari (2003)	Serfling regression	3 year serial regression minus last 2 weeks	Serfling regression	95% upper confidence interval
Gesteland (2003)	Recursive least squares adaptive filter	Less than 1 week	Less than 1 week	95% upper confidence interval
Mostashari (2003)	Serfling regression	Not specified	Serfling regression	99% upper confidence interval
Reis (2003)	Autoregressive integrated moving average	Not specified	Autoregressive integrated moving average	7 day detection filter
Thompson (2003)	Poisson regression	Not specified	Poisson regression	
Viboud (2003)	Method of analogues	Not specified	Method of analogues	None
Heffernan (2004)	Satscan temporal, temporo-spatial	14 day baseline minus 1,2,or 3 day window	14 day baseline	Scan statistic
Kleinman (2004)	General linear mixed model	Not specified	Census estimates	Most unusual cluster area
Miller (2004)	Autoregressive error model	Not specified	Autoregressive error model	CUSUM

Table 13. (Continued)

Study (Year)	Analysis	Length of Baseline	Baseline	Anamoly
Rogerson (2004)	Cumulative sum control chart	Not specified	"Regional" logistic regression	Cumulative sum control chart
Kulldorff (2005)	Satscan space time permutation	30 day moving window	None	Scan statistic
Hutwagner (2005)	EARS	7 day moving average	7 day moving average	EARS
Hutwagner (2005)	EARS	7 day moving average; 5 years	7 day moving average; 5 years	Seasonally adjusted EARS
Brillman (2005)	Least squares regression	8 week window	Least squares regression; EWMA	Page's test
Besculides (2005)	Cumulative sum control chart; SatScan	Not specified	Serfling regression	14 day CUSUM + SatScan
Ritzwoller (2005)	General linear mixed model	Not specified	General linear mixed model	Scan statistic and SMART score
Wang (2005)	Autoregressive periodic model	Not specified	Autoregressive periodic model	2 standard error of prediction
Vergu (2006)	Poisson regression	Not specified	Poisson regression	
Wong (2006)	Poisson regression	Not specified	Poisson regression	
Jackson (2007)	General linear model	3 years	General linear model	Probability from poisson distribution
Cooper (2007)	Poisson regression	Not specified	Poisson regression	Empirically derived threshold
Haug (2007)	Exponential weighted moving average	Not specified	"Regression"	95% upper confidence interval
Cooper (2008)	Satscan space time permutation	4 months	None	Scan statistic
Meyer (2008)	Cumulative sum control chart	7 days; 3-9 days; 4 weeks	1-12 months historical average	Cumulative sum control chart
Flamand (2008)	Shewhart control chart	Not specified	7 day moving average	2 standard deviations
Meyer (2008)	Cumulative sum control chart	Not specified	Poisson regression	Farrington exceedence Score
Najmi (2009)	Adaptive recursive least squares	4 week memory factor	Adaptive recursive least squares	Not Specified
Tokars (2009)	EARS	7 day moving average	7 day moving average	EARS
Cami (2009)	Regression based aggregation	8 week moving average	8 week moving average	Cumulative sum control chart

5.3.5 Baseline

The first step in detecting outbreaks is to estimate the expected level of disease activity in the population being monitored - the baseline. (233) This is true in traditional or syndromic surveillance. An important consideration for calculating a baseline is the amount of data available for analysis. Long baselines may demonstrate predictable trends over the course of years: secular trends accounting for the movement of population centers or health care utilization (234), seasonality (234), environmental conditions such as high pollen periods (235), or periods of co-circulation of organisms (236,237). These trends may increase the rate of illness in the monitored population but not beyond what is regularly expected. When considering long baseline periods, investigators often develop regression models with terms to adjust for known trends in the data to better predict the current level of disease activity. Enhancements to regression models may also consider past outbreaks and serial autocorrelation of the data. (238,239) Models such as this Serfling type have been developed for syndromic surveillance of febrile and respiratory illness. (240,241,242,243,244,245,236,237,223) A complete listing is available in **Appendix D.**

Regression methods require long baseline periods and intimate understanding of the underlying data to build the most accurate statistical models to estimate the baseline. Time series methods such as moving averages, stratified moving averages, and cumulative summation techniques require shorter baseline periods but may still adjust for regular patterns within the underlying data. In rapidly evolving scenarios, such as surveillance in the wake of bioterrorism in 2001, the need may arise for the use of a new data stream for which little baseline data is

available. (246) **Figure 7** illustrates several features of baseline calculation using relatively short periods of time appropriate for bioterrorism surveillance.

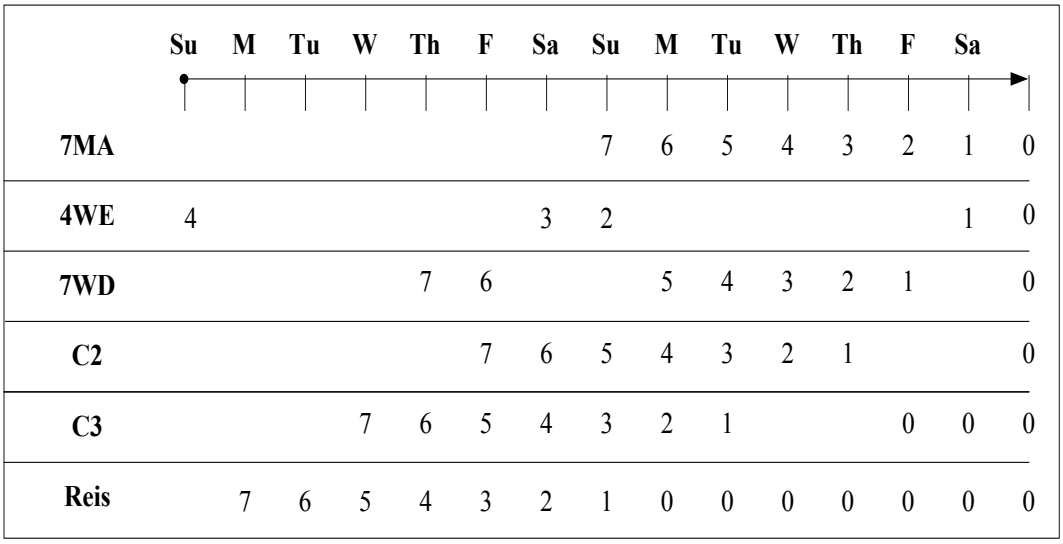


Figure 7. Several Examples of Baseline Calculations

Each numbered day contributes to the baseline. The day numbered '1' corresponds to the first day of the baseline. '0' days are used to calculate the observed. The simplest case is to calculate a 7 day moving average (7MA) to calculate the mean and standard deviation of the number of incident cases. A 7 day baseline with a 2 day buffer (C2), the Early Aberration Reporting System (EARS) approach, was developed by CDC investigators to assure that recent outbreak effects do not bias the baseline upward (247,248) A 7 day baseline with a 2 day buffer using 3 days to calculate the observed number of cases (C3) is employed by EARS developers to identify more slowly developing outbreaks. Reis et al have employed a one week weighted window to calculate the observed thus pushing the baseline back by 7 days. (251,252) The four day weekend baseline (4WE) is adjusted to only consider Saturdays and Sundays as health care resource utilization often differs significantly from weekdays. The seven day weekday (7WD)

baseline complements this approach by only using weekdays to calculate the baseline parameters. (249)

5.3.6 Test statistic

The next step in syndromic analysis is to generate a statistic assessing the difference of the observed value from the expected value. (250) Reis et al. developed a filter approach which computes a test value for one day, 7 day, 7 day linear, and 7 day exponential filters. (251) For each filter, a weighted sum is calculated over a 7-day sliding detection window. The forecast errors on each day are then multiplied by the filter weights of the corresponding days of the sliding detection window. These products are then summed to form the overall detection score for each filter. If this score exceeded a predefined threshold, an alarm is triggered. (252)

Burkom demonstrated an effective alerting algorithm using a z-score as the test statistic when counts are sparse or data history is short. (253) A z-score can be derived by subtracting the population mean from an individual raw score and then dividing the difference by the population standard deviation. The z-score indicates how many standard deviations an observation is above or below the mean. The z-score is often applied to the prediction residuals (observed minus the expected count) with the mean of a predetermined number of days of residuals subtracted from the current estimate and divided by the standard deviation of that number of days.

The popular EARS methodology developed at the CDC features a cumulative summation (CUSUM) technique. CUSUM is applied to the z-score of forecast residuals. (254) When the CUSUM exceeds a predefined threshold, 4 is often used, an alarm is sounded and the CUSUM is reset to 2. (255)

5.3.7 Control Charts

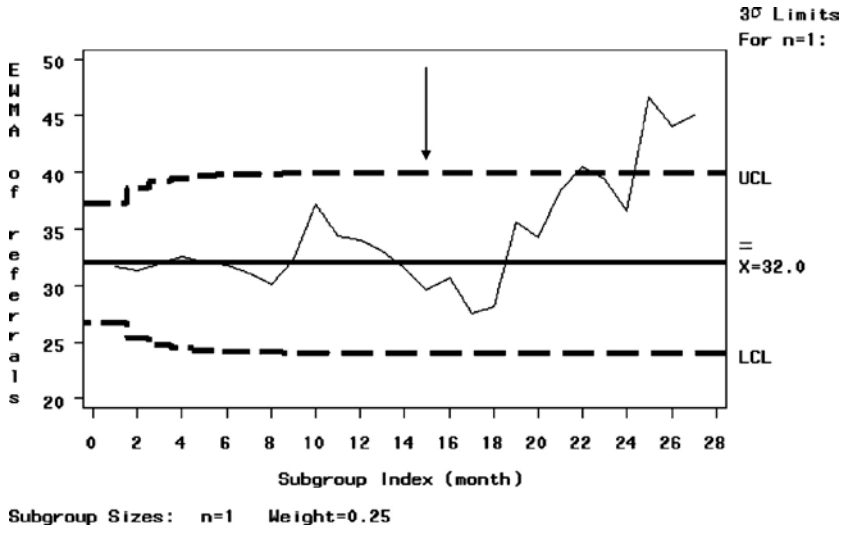


Figure 8. Example Control Chart

The Shewhart control chart, often referred to simply as control chart, is a graphical and analytical tool for deciding whether a process is in a state of statistical control. (256)In this case, a control chart is used to distinguish a typical disease outbreak from bioterrorism related illness. An example control chart from Noble et al. is shown in **Figure 8**. (257)

A Shewhart chart specifies control limits in terms of a multiple of the standard error of the plotted summary statistic or as probability limits. The central line on a Shewhart chart indicates the average (expected value) of the summary statistic when the process is in statistical control. The upper and lower control limits of a control chart indicate the range of variation to be expected in the summary statistic when the process is in statistical control. The control limits are commonly computed as 3σ limits representing three standard errors of variation in the summary statistic above and below the central line. (258) Control chart method examples for syndromic surveillance are employed by Rogerson, Cami, and Meyer. (259,207,211)

An exponentially weighted moving average (EWMA) control chart, as shown in **Figure 8**, approach is popular with syndromic surveillance practitioners because it weighs recent events more heavily than those further back in time. This is especially useful if calibrating a system for rapidly unfolding incidents as opposed to slowly developing events. EWMA specifies the weight assigned to the most recent day's mean in the computation of the moving average. (253) It can be used to compute control limits from the data based on a multiple of the standard error of the plotted EWMAs. EWMA smoothes a prediction residual using a smoothing coefficient. The closer the value is to 1, the more weight is applied to the first day of residuals. A common value for the smoothing coefficient is 0.4. A z-score is then calculated scaling for the length of the baseline used. A good example of this technique in practice is documented in Hogan et al. (212)

5.3.8 Evaluation of syndromic surveillance systems

To evaluate the effectiveness of a system, investigators often attempt to prospectively or retrospectively identify outbreaks. **Table 14** provides a summary of validation approaches and their chosen evaluation measure.

Table 14. Syndromic Surveillance Validation Approaches

Study (Year)	Validation	Evaluation Measure
Serfling (1963)	Seasonal influenza	Correlation with seasonal illness
Choi (1981)	None	Absolute percentage error; Serfling regression results
Costaglia (1991)	Seasonal influenza	Correlation with seasonal illness
Carrat (1998)	Seasonal influenza	Correlation with seasonal illness
Toubiana (1998)	Seasonal influenza	Sensitivity; Specificity
Tsui (2001)	Seasonal influenza	Sensitivity; Specificity; Timeliness
Lazarus (2002)	Seasonal influenza	Correlation with seasonal illness
Lewis (2002)	Seasonal influenza	Correlation with seasonal illness
Gesteland (2003)	Investigation	Signals reviewed
Hogan (2003)	Seasonal influenza	Timeliness; Signal strength
Mostashari (2003)	Seasonal influenza	Correlation with seasonal illness
Viboud (2003)	Seasonal influenza	Correlation coefficient between observed and expected
Heffernan (2004)	Seasonal influenza	Signals reviewed; Correlation with seasonal illness
Rogerson (2004)	Seasonal influenza	Differences in geographical spread of clusters
Besculides (2005)	Seasonal influenza	Signals reviewed; Correlation with seasonal illness
Kulldorff (2005)	Seasonal influenza	Signals reviewed; Correlation with seasonal illness
Ritzwoller (2005)	Seasonal influenza; Chart review	Signals reviewed; Correlation with seasonal illness
Vergu (2006)	Seasonal influenza	Forecast accuracy versus seasonal illness.
Cooper (2007)	Positive influenza tests	Correlation with seasonal illness; Time lag until alarm
Haug (2007)	Seasonal influenza	Correlation with seasonal illness
Cooper (2008)	Seasonal influenza	Signals reviewed; Correlation with seasonal illness
Flamand (2008)	Seasonal influenza	Correlation with seasonal illness
Meyer (2008)	Investigation	Signals reviewed
Cami (2009)	Seasonal influenza	AMOC curves (mean week of detection versus false alarms per year)

Attempts to investigate each outbreak signaled by syndromic surveillance can be labor intensive and often do not uncover outbreaks beyond clusters of seasonal or naturally occurring illness. Studies of signal investigations are summarized in below in **Table 15.**

Table 15. Syndromic Surveillance Signal Investigations

Study	Result
Hanslik	19 signals investigated using a 99.7% upper confidence interval threshold.
Heffernan	14 of 22 citywide respiratory signals investigated; 21 of 22 citywide fever signals during peak Flu A and Flu B season investigated.
Meyer	79 signals investigated from 4 sources. No actual outbreaks.
Mostashari	45 alarms investigated; 21 during flu season.

For a syndromic surveillance designed to detect bioterrorism, there is little or no opportunity to prospectively identify outbreaks. Investigators may use historical or naturally occurring outbreaks such as influenza. (260) However, there is typically only one outbreak per year requiring many years of data. Also, the size, shape, and duration of the outbreak do not necessarily replicate a bioterrorist attack.

Simulated outbreaks provide investigators the opportunity to vary the size, duration, and distribution of cases over time. A typical approach is to use an existing data source such as ED visits and 'inject' excess cases as outbreaks into the time series. (260) Injects can vary by size by using absolute number, percent above baseline, or a number of standard deviations above baseline. Simulations often use the standard deviation of the underlying time series to generate the magnitude of the outbreak. Other simulations use a fixed number of cases added to the underlying time series. (261)

A synthetic outbreak may vary the distribution of cases in time: one day, linear, exponential, reverse exponential or random distributions are all good examples. In this way hundreds of outbreak scenarios may be evaluated while considering factors such as timeliness or the size of the outbreak detected. Other factors such as the start date of the outbreak or time between outbreaks injected into the time series may also be randomized to further add to the evaluation. Common measures for outbreak detection are the percent of outbreaks detected, sensitivity, specificity, and the area under the curve (AUC) for a receiver operating curve (ROC). Results are often stratified by the timeliness of the outbreak detection or by the size of outbreaks detected.

5.4 SYNDROMIC SURVEILLANCE FOR ANTHRAX

Current inhalation anthrax monitoring approaches began as surveillance for indicators of respiratory illness, fever, or a combination of both. (205) However, it became apparent that investigators were more likely to identify seasonal influenza than attacks of bioterrorism. **Figure 7** and **Figure 9** below illustrates the correlation between positive influenza A and B tests with the increase in influenza like illness in New York City for the 2010-2011 influenza season. In addition, recent studies by Betancourt (262), Begier (263), Beitel (264), and Marsden-Haug (265) showed the highest percentage of illnesses to be attributed to diagnoses of acute upper respiratory infection not otherwise specified (NOS), Acute pharyngitis, and unspecified viral infection which all exhibit high seasonality.

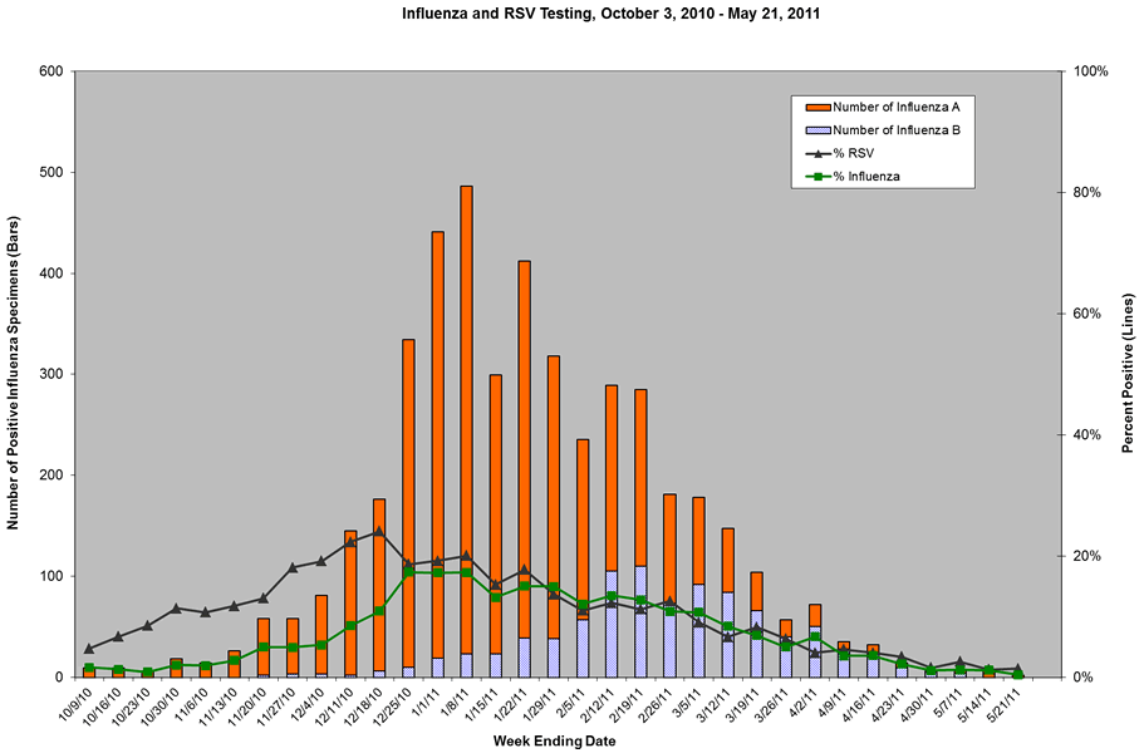


Figure 9. New York City Influenza and RSV Testing, 2010-2011 Season

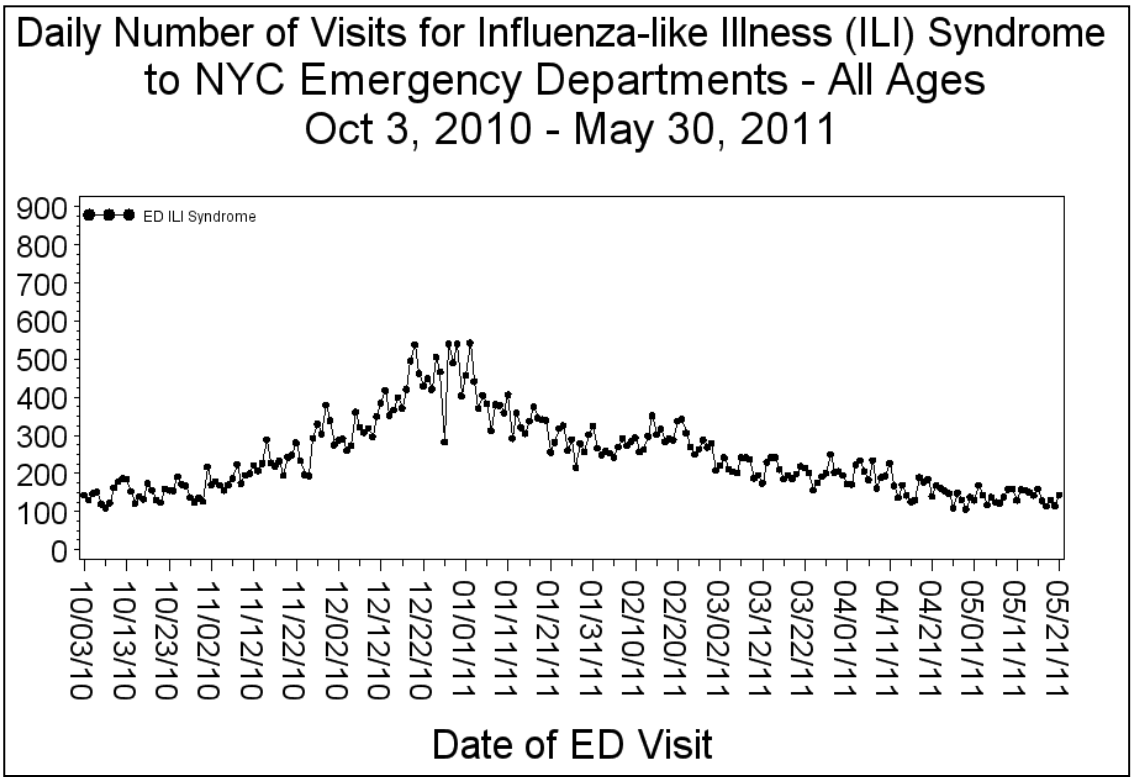


Figure 10. New York City Influenza-Like Illness Surveillance

Targeting late phase inhalation anthrax-specific monitoring would complement the large scale febrile illness syndromic surveillance most health departments currently practice. As demonstrated in the wake of the 2001 anthrax attacks, the system would monitor for fulminate stage clinical findings of inhalation anthrax such as acute respiratory distress and mediastinal widening. Most systems already collect the necessary data types for identifying inhalation anthrax. Respiratory distress is often defined by the use of ICD-9 codes 518.5, 518.81, or 518.82 or an ICD-9-CM procedure code for the use of a mechanical ventilator 96.7. (266)

Radiology notes, while not widely collected but readily available, would be used to identify mediastinal changes using natural language processing (NLP) techniques. A recent Chapman study examined 1 year of radiologic report data to evaluate the accuracy of NLP

techniques for identifying mediastinal widening in full-text records. (216) The NLP technique was validated by chart review. The study examined 79,032 records and classified 1,729 (2.19%) as WM. The sensitivity was found to be 85.6, Specificity=97.2, PPV=40.9. The final classifying terms are shown in **Table 16.** This study shows promise for investigators looking for more accurate means of identifying late phase inhalation anthrax symptoms from textual data types.

Table 16. Terms for Identifying Mediastinal Widening

Concept type	Terms
Boolean	"bihilar" or "bronchial lymph node" or "bronchial" or "hilar lymph nodes" or "hilar lymph node" or "hilar" or "hila" or "hilum" or "mediastinal lymph nodes" or "mediastinal lymph node" or "mediastinal" or "mediastinum" or "paramediastinal" or "paratracheal lymph nodes" or "paratracheal" or "peritracheal" or "tracheobronchial lymph nodes" or "tracheobronchial"
Boolean	"enlarged lymph nodes" or "lymph node enlargement" or "lymphadenopathy" or "widened" or "widening" or "wide"
Probabilistic	"lymphadenopathy (negated)" or "mediastinal lymph node (negated)" or "mediastinal lymph node enlargement (negated)" or "mediastinal lymphadenopathy (negated)" or "mediastinal widening (negated)"
Probabilistic	"hilar lymphadenopathy" or "mediastinal lymph node enlargement" or "mediastinal lymphadenopathy" or "mediastinal widening"

5.5 EVALUATION OF CURRENT SYNDROMIC SURVEILLANCE FOR INHALATION ANTHRAX

Currently systems rely on monitoring for febrile illness or respiratory syndromes to detect the largest releases of inhalation anthrax. Three published systematic evaluations of current systems give evidence of the strengths and weaknesses of the approach using the working surveillance systems data in Washington state, Florida, and US military treatment facility data from 10 centers around the US (268,267,269).

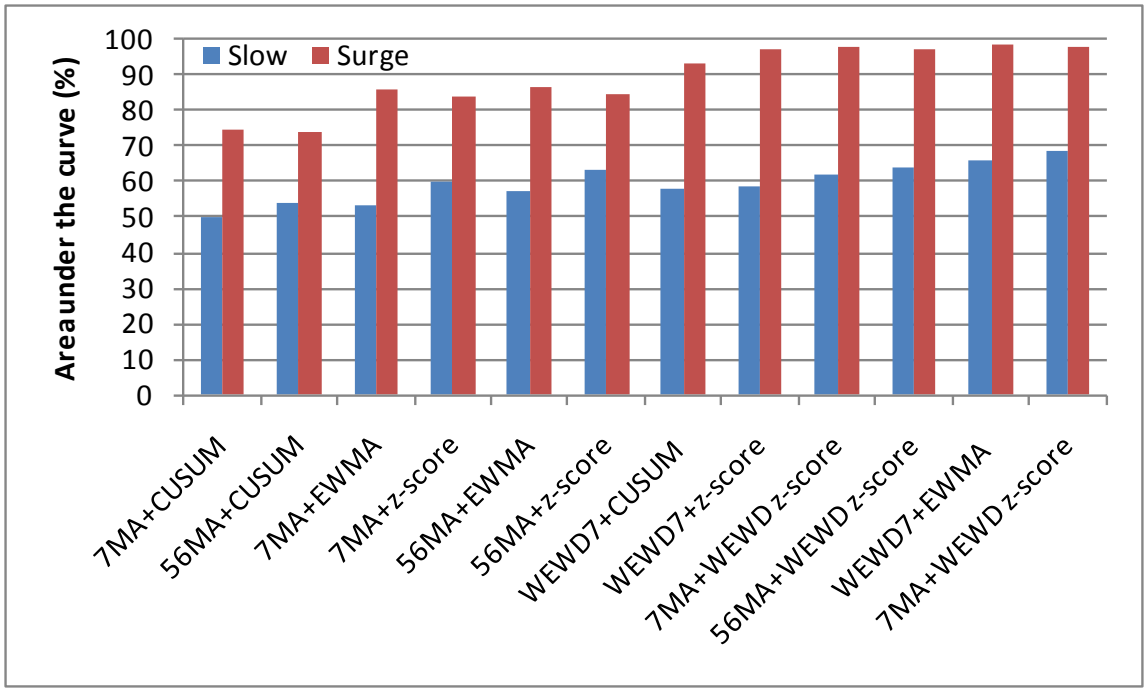


Figure 11. Area Under the Curve Varies by Outbreak Type, Baseline, and Test

Murphy examined outbreaks of 1, 2, 3, and 4 times the standard deviation of baseline activity. (267) The results are presented in **Figure 11**.

A 'surge' outbreak was represented by a spike of cases over 1 – 3 days. Murphy combined different baseline approaches with different statistical tests: single day z-score (z-score), 28 day CUSUM (CUSUM), or a 28 day EWMA with coefficients' set at 0.4 or 0.9 (EWMA). The study found slowly developing outbreaks are more difficult to detect than surge outbreaks. The percentage of slowly developing outbreaks detected ranged from a worst performance of 7MA+CUSUM (50.02%) to a best performance of 7MA+WEWD (68.69%). The percentage of surge outbreaks detected ranged from a worst performance of 56MA+CUSUM (74.01%) to the best performance of WEWD7+EWMA (98.78%).

The top performing tests adjusted for weekends in either the baseline calculation or test itself. The worst performing algorithm used the shortest baseline without adjustment for weekends and the CUSUM which only considers the current day's observation. The best performing slow outbreak combination used a short baseline but the WEWD z-score used residuals from the previous 28 days. Surge outbreaks were best detected by methods which adjusted for weekends and considered single days when testing the observed versus the expected. Four methods exceeded 97% AUC.

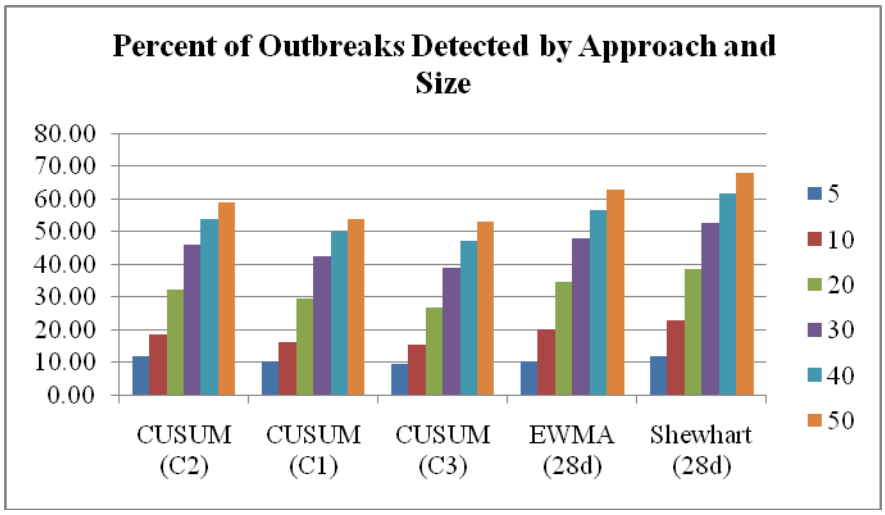


Figure 12. Percentages of Outbreaks Detected Varies by Approach and Size

Jackson examined outbreaks corresponding to five simulated distributions in time: airborne bioweapon, point-source, community transmission with close contact, multi-modal community transmission, and airborne community transmission. (268) The study used original time series from healthcare facilities. Indicator with mean indicator volume (Standard Deviation) were as follows: Respiratory 60 (16.0), Influenza-like illness 35 (9.9), Asthma 10 (4.0), and

pneumonia hospitalizations 2 (1.6). Outbreaks lasted 1, 2, 4, 6, 8, 16, and, 32 days. The results are presented in **Figure 12**.

The magnitude of outbreaks varied from 1 – 4 times the standard deviation of the time series which corresponds to 5-50 additional cases. The study found that smaller outbreaks are harder to detect than large. The outbreaks were from 250% increase for pneumonia hospitalizations to an 8% increase for Respiratory syndromes. The 28 day Shewhart method appeared to perform the best but not by a large amount.

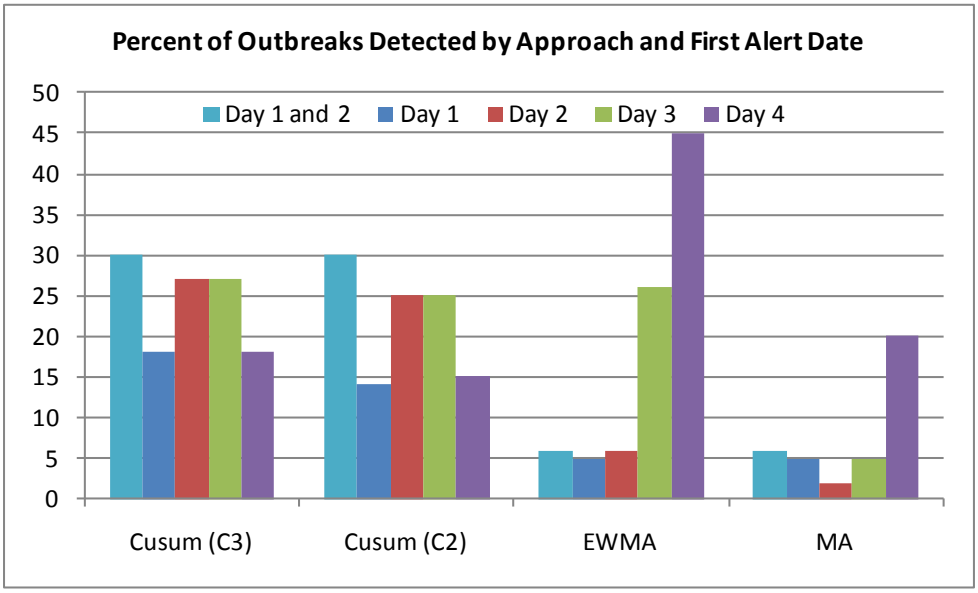


Figure 13. Timeliness of Detection for Slowly Building Outbreaks

In a recent study comparing multiple outbreak detection methods, Zhu compared the timeliness of various approaches. (269) Simulated outbreaks peaked on day 4 to three times the baseline and decreased to baseline rate by day 8. The study found slower outbreaks are best detected by EWMA which weights events over time. EWMA performed best on the fourth day. The results are presented in **Figure 13.** The study found the best performance for first day detection by C3 (18%), second day by C2 (25%) and C3 (27%), third day was similar (~25%) for

EWMA, C3 and C2. By the fourth day EWMA (45%) performed the best. EWMA on the fourth day had the highest percentage of all methods on any day.

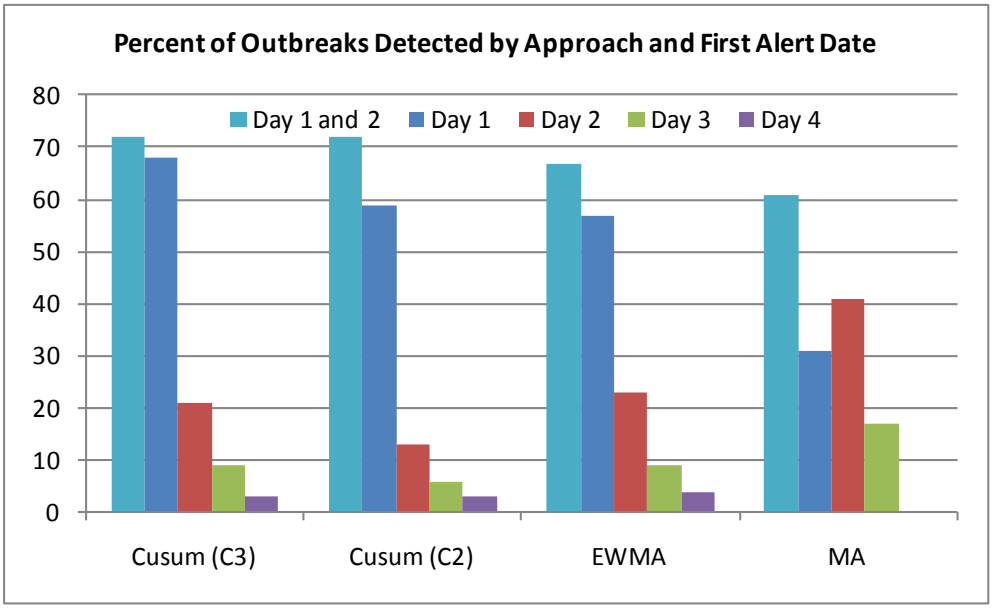


Figure 14. Timeliness of Detection for Surge Outbreaks

For surge outbreaks, cases were increased to 3 times the baseline rate on day 1-day 4 and decreased back to baseline over days 5-8. The study found that surge outbreaks were easier to detect than slow. The results are presented in **Figure 14.** The best performance was seen by C3 and C2 for signaling on day 1 and day 2. For day 1 signal, C3 performed best. After first day performance, the performance of all approaches seriously decrease except for simple moving average which would apply a constant weight to the outbreak date until the end of the moving average window.

6.0 SUMMARY OF THE LITERATURE REVIEW

Surveillance for naturally occurring anthrax, of all varieties, is a well-established practice. Patients present to healthcare professionals with distinct clinical findings consistent with the disease. More importantly, the history of present illness will reveal exposure to a known vector of anthrax such as sick livestock, contaminated hides, or wool of an exotic origin. However, the case of anthrax of an unknown origin presenting to the Emergency Department requires a quick and substantial public health response of treatment, prophylaxis, and decontamination. Public health authorities must enhance monitoring to identify additional anthrax cases in the event of an intentional release of aerosolized anthrax. Syndromic surveillance, the widely accepted monitoring approach for bioterrorism, effectively monitors for large scale, wide-area events. However, the 2001 anthrax letters event revealed a considerable gap in the ability of syndromic surveillance to work effectively for small events. Small events of bioterrorism, while low in scale, often cause a disproportionate amount of terror, anxiety, and cost to the public.

The literature review shows that strong work is currently underway to identify more effective syndromic surveillance approaches for recognizing anthrax cases. The recent work by Chapman et al. proposes that surveillance should focus on recognizing widened mediastinum findings in textual data. (276) Kyriacou et al found that a high rate of accuracy for identifying inhalation anthrax could be obtained using an algorithmic approach based on key clinical data such as a chest radiograph, history and physical, and laboratory results available from Emergency Department encounters. (156) Lastly, Jackson showed that improvement in anthrax surveillance can be attained by systematically combining a variety of baseline calculations with

aberration detection methods, depending upon the scenario, size of the outbreak, and timeliness requirements. (268) These studies, along with other developments in the field, show that syndromic surveillance has moved beyond the initial paradigm of embattled health department waiting for a post-9/11 terrorist attack. The practice now incorporates sophisticated data processing, clinical studies, and analytical techniques.

Gaps in the literature indicate that further study on identifying potential outbreaks of inhalation anthrax using syndromic surveillance is merited. For example, tools for identifying patients presenting with syndromes of severe respiratory findings and mediastinal widening (key components of inhalation anthrax) need further development. Patients with these syndromes differ from those currently targeted by syndromic surveillance systems and, thus, will require a modified monitoring strategy. As an illustration, the textual chief complaint data fields that health departments currently rely upon in syndromic surveillance are a poor source for identifying subjects with later stages of inhalation anthrax. Chief complaints often contain only one clinical finding and, thus, prevent investigators from using anything but the simplest case definitions such as “chest pain” OR “anthrax” OR “white powder” in their searches. The popular approach available from the New York City Department of Health and Mental Hygiene illustrates the limitations. (270) The use of more sophisticated data fields and an algorithmic approach may address these limitations, leading to more accurate, useful syndromic surveillance for inhalation anthrax. However, the value of advanced tools has not yet been established through validation studies.

7.0 PURPOSE AND SPECIFIC AIMS OF THE STUDY

The current approach for syndromic surveillance for inhalation anthrax evolved in the aftermath of the September 11th attack which introduced the very real possibility of large-scale biological attack affecting thousands of people. The reality of the ensuing public health situation was that 22 persons were infected, 6 fatally, and that millions were affected directly or indirectly by experiencing terror and anxiety. This smaller attack lead to less infected persons and lower fatalities than expected in the post 9-11 climate, but nevertheless presented a new challenge to public health. If one person or a small group of actors could use the US Mail system to spread disease and terror, surveillance must be readied to detect that threat as soon as possible. The proposed study seeks to improve the currently accepted practices of high-volume, regional syndromic surveillance for inhalation anthrax using a more focused, hospital-based approach featuring a more exact case definition.

The public health significance of this work unfolded on a national stage over a decade ago when an intentional release of aerosolized anthrax spores resulted in twenty two cases of anthrax. This act of bioterrorism caused 11 cases of cutaneous anthrax and 11 cases of inhalation anthrax with 6 of the inhalation anthrax cases being fatal. (271) Although this number of anthrax cases represents a tiny fraction of the US population, the implications for the nation were extensive. The investigation, prophylaxis, and subsequent clean-up from the anthrax release carried a financial cost in the millions of dollars. In addition, the event created a sense of terror for millions of American citizens.

The following study seeks to investigate the effectiveness of syndromic surveillance for monitoring bioterrorism-related anthrax in an emergency department population. Current

surveillance practice relies on casting the widest possible net for anthrax by concentrating on influenza-like illness symptoms. These symptoms are a possible early indicator of anthrax. However, they also may identify other health events, and, as a result, this surveillance approach for anthrax often leads to frequent false alarms. The following study seeks to improve anthrax outbreak detection by examining the effectiveness of an approach which relies on identifying symptoms and syndromes in anthrax patients that occur slightly later in the course of their illness. The rationale of this approach is to target symptoms that are more anthrax-specific, thus considerably reducing the number of outbreaks to investigate for confirmation.

7.1 SPECIFIC AIM 1

To identify a cohort of anthrax-like illness among individuals using the Emergency Department (ED) at Presbyterian University Hospital (PUH) in 2001. Syndromic surveillance is typically conducted in hospital Emergency Departments (ED). The first step in the evaluation of syndromic surveillance of anthrax in an ED setting requires the identification of admission events that would draw the attention of a syndromic surveillance program. The aim will develop a case definition for inhalation anthrax based upon fulminate phase syndromes and symptoms, ICD-9-CM codes, arterial blood gas levels, and radiologic reports to identify mediastinal widening or lymphadenopathy on chest radiographs in an ED setting. Compared to the predominant case definition of inhalation anthrax in the literature, based on indications of febrile illness and chest pain, the proposed case definition is more encompassing, and includes more specific and later stage health events in the natural history of anthrax. The assumption is that this comprehensive case-definition will greatly reduce the number of incorrect patient encounters

included in the surveillance effort, while not sacrificing timeliness of detection to a significant extent. Information from the medical records on all ED admissions in 2001 will be reviewed to identify the number of persons who meet the proposed case-definition.

7.2 SPECIFIC AIM 2

To identify and characterize the clinical characteristics which differentiate inhalation anthrax from other causes of acute respiratory failure with a widened mediastinum. An important component of this work is to examine the usefulness of existing medical record information for syndromic surveillance purposes. This aim will compare the reported signs, symptoms, medical history, and laboratory values for the emergency department patients meeting the fulminate phase syndromic case definition from Specific Aim 1 to the clinical characteristics of the 11 inhalation anthrax patients from the 2001 terrorism event in order to determine which clinical features are most useful in discriminating inhalation anthrax from other causes of acute respiratory failure among individuals with evidence of a widened mediastinum. This aim will also address the findings from the literature that signs and symptoms primarily associated with seasonal influenza such as sore throat or runny nose would most significantly contraindicate inhalation anthrax. Other findings from the medical history of the patient will also be examined to identify and evaluate potential factors that can be used in syndromic surveillance to rule out anthrax.

7.3 SPECIFIC AIM 3

To simulate outbreaks of anthrax like illness based on the characteristics of the 2001 anthrax attacks.

Epidemiologists use known outbreaks to assess the usefulness of their syndromic systems. The evaluation of syndromic detection methods and their usefulness requires the identification of known outbreaks. Because only one anthrax outbreak has occurred in the recent past, simulation techniques must be used to recreate outbreaks based on the 2001 attack. To simulate an outbreak of inhalation anthrax during the study period, excess cases, based on the pattern of the cases from 2001, were added to the daily counts from the 2001 PUH admissions. This aim is required to assess the accuracy and timeliness of the outbreak detection methods in Aim 4. This aim replicated a set of outbreaks consistent with anthrax outbreaks by varying the magnitude, duration, and distribution of excess cases. This aim applied simulation methods demonstrated in the syndromic surveillance literature used for detecting large influenza like illness outbreaks. Although smaller in scale, a useful set of synthetic anthrax outbreaks was produced by this aim.

7.4 SPECIFIC AIM 4

To determine the potential accuracy and timeliness of commonly used detection methods for inhalation anthrax outbreaks.

In order for public health practitioners to appropriately respond to inhalation anthrax outbreaks, they must understand the accuracy and timeliness of the alerting syndromic

surveillance system. This is especially true in the case of a newly implemented syndromic surveillance system. The goal of this aim is to evaluate the potential accuracy and timeliness of a fulminate phase inhalation anthrax syndromic surveillance system. The simulated outbreaks constructed in Specific Aim 3 will be evaluated using the z-score, and the cumulative summation (CUSUM) algorithms used by the CDC Early Aberration Reporting System (EARS) to assess accuracy. The time to detection will also be compared across methods to better understand how quickly outbreaks can be detected.

8.0 METHODS

This research was undertaken using data collected from the emergency department of the PUH. The following section describes the methods of the study in more detail; including the study population, details on the case definitions, data collection, and data analysis. The University of Pittsburgh Institutional Review Board reviewed and approved this study (**Appendix H**).

8.1 STUDY POPULATION

8.1.1 Inclusion Criteria

This study identified patient visits resembling those of individuals seeking care for critical symptoms of late stage anthrax. Eligible visits for this study were selected from a review of all ED admissions to Presbyterian University Hospital (PUH) in 2001. Eligible visits were classified as those visits with criteria resembling inhalation anthrax. Specifically, eligible visits had to meet the following syndromic case definition for inhalation anthrax: *any patient admitted to PUH from the ED with acute respiratory failure and radiological findings consistent with inhalation anthrax.*

Patient visits with acute respiratory failure were identified using clinical laboratory values, diagnostic codes, and procedure codes. A review of consensus statements, medical textbooks, and primary literature provided resource material for the inclusion criteria for the study. Acute respiratory failure was defined as any one of the following: a PCO_2 value of ≥ 50

mmHg and pH of <7.38, a PO_2 of <60 mmHg, a diagnosis of ARF (ICD-9 518.81) in the Admission, Discharge, and Transfer (ADT) record, mechanical ventilation (ICD-9 96.7 or ICD-9 96.72), or intubation (ICD-9 96.04). Only acute respiratory failure that occurred within 48 hours of admission was included. Once it is determined that a patient visit met the definition of ARF, their free text radiology reports were retrieved. (141,272, 273, 274, 275)

Radiological findings of anthrax were covered extensively in section **4.2 Clinical Features.** Radiological findings consistent with inhalation anthrax were defined as mediastinal widening or mediastinal, paratracheal, and hilar lymphadenopathy on chest radiograph, chest CT, or chest MRI as described by Inglesby. (145) Only radiological findings consistent with inhalation anthrax occurring within 48 hours of admission were considered. Confirmation of these findings was provided by radiologist review. Review of radiological records is described in the following section.

The "Identifying Patient Sets" software was used to formulate Boolean search strings (e.g. "mediastinal AND widening") to identify patient visits with possible mediastinal widening or lymphadenopathy (IPS Software, IAIMS Program at the University of Pittsburgh's Department of Biomedical Informatics). (276) All radiology reports were retrieved for 4 patient sets: mechanical ventilation, intubation, a diagnosis of ARF, or arterial blood gases meeting the inclusion criteria. For each of these four sets Boolean search strings were formulated to retrieve the maximum amount of potential patient visits meeting the radiological criteria ("Hits"). All reports which contain a word or phrase related to mediastinal widening or lymphadenopathy were reviewed preliminarily. Any report which only mentioned these findings in a statement of negation ("The patient had no mediastinal widening") or in relation to verifying tube placement ("An endotracheal tube, right IJ swan ganz catheter, mediastinal drainage tube, and left chest

tube are in place") were labeled as 'Not of interest' ("Misses"). All other reports were given to radiologists for further review.

To identify findings consistent with IA, radiologists were recruited from the University of Pittsburgh Department of Radiology residency program and paid on an hourly basis to read the radiology reports identified by the software. In an attempt to improve internal validity and reduce measurement error, the study required that each radiologist attend at least one training session. Initial training consisted of a one hour session and review of a ten record training set. A detailed instruction for Form 1 is included in **Appendix I.**

Radiologists reviewed all chest radiographs from the patient's first three days of admission. Radiologists characterized each report as positive, negative, inconclusive, or not specified for mediastinal widening or lymphadenopathy. See **Appendix J**. Reviewers further characterized lymphadenopathy into anatomical locations. Only hilar, mediastinal, and paratracheal lymphadenopathy were accepted as radiological findings that could be consistent with inhalational anthrax for the purposes of this study. Once all records were reviewed by two radiologists, a third radiologist broke the tie for discordant reports. Radiologist agreement will be reached through majority consensus. See **Appendix K.**

Radiologists did not accept mediastinal widening that was attributed to positioning, technique, or was mentioned as a historical finding. Other findings which were not accepted or considered controversial: calcified lymph nodes, mediastinal shift, soft tissue mass, huge edema in the chest and "limited studies." CT scans are considered more informative than chest X-rays but both were accepted.

Eligible patient visits had to meet three successive criteria to be included in the anthrax like illness population. The process for identifying a patient visit is illustrated in **Figure 15**.

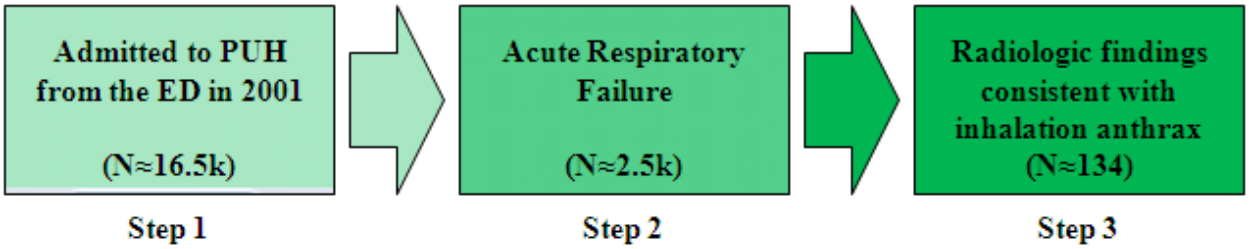


Figure 15. Flow Chart of Study Inclusion Criteria

Patient visits that met all study inclusion criteria will be referred to as "syndromic" patient visits and their condition will be described as "anthrax like illness' for the remainder of the paper. The number of patient visits in the PUH ED that would be expected to be identified in a syndromic surveillance system (with the forementioned eligibility criteria) will be referred to as the "PUH baseline" for the remainder of the paper.

8.1.2 Data collection

Detailed clinical data was collected for all (N=134) patients meeting the study inclusion criteria. Data for this study were obtained from the University of Pittsburgh Medical Center (UPMC) Medical Archival Retrieval System (MARS). This electronic medical records system includes data from hospital and emergency department visits for the PUH and other clinical units in the UPMC health system. Data collection consisted of examining both textual reports and coded data. Not all patients had complete records for all types of information. This may be due to very short ED episodes where the patient was essentially passed through to critical care, missing chart information, or only a paper version but no electronic version exists. Two resident,

emergency medicine physicians were recruited and trained to review the physical findings and medical history portions of the patient's ED report, and additional textual reports.

The two ED physicians reviewed each ED report for the presence of fever, sweats, fatigue, cough, dementia, dyspnea, nausea or vomiting, chest pain or discomfort, myalgias, headache, confusion, abdominal pain, sore throat, rhinorrhea, and trauma. The reviewing physicians also collected chief complaint. The complaint was either explicitly stated in the report or assigned by the reviewing physicians. The residents were trained in a one hour session with ten training reports and were paid an hourly rate for reviewing reports. All reports identified in an initial eligibility screen were reviewed by both residents. Ties were broken by consensus during a three hour long conference at the end of record review. Detailed instructions given to the residents and can be found in **Appendix L.**

To better understand the cause of admission, ED physicians collected medical history from the patient's ED report. The Charlson Index, a weighted index that takes into account the number and the seriousness of comorbid diseases, was used to categorize important conditions from the patient's medical history. (277) Each item of the history was classified by an emergency medicine physician as one of 17 categories of the Charlson Index. A supplement to the instructions provided an expanded listing of conditions includes each medical history definition as adapted by Deyo et al. (278) See **Appendix M.** Those include chronic pulmonary disease, cerebrovascular disease, renal disease, peripheral vascular disease, rheumatologic disease, diabetes, myocardial infarction, congestive heart failure, dementia, peptic ulcer disease, mild liver disease, hemiplegia or paraplegia, any malignancy, moderate or severe liver disease, metastatic solid tumor, or AIDS. Only pre-existing conditions of the admitted patient were included. Reviewers excluded complications developed during the hospital stay. Reviewers

recorded any additional medical history items mentioned in the patient's ED report that fulfilled the definition of a comorbid condition in an 'additional history items' field.

In addition to the radiological findings required as part of the study inclusion criteria, a second review of the radiological records was conducted to ascertain presence of findings consistent with inhalation anthrax. Patient free text radiological records were reviewed by radiologists for the presence of consolidation or pleural effusions. See **Appendix S**. The reviewers further characterized each record by lung and region. Tie-breaking consisted of a reviewer conference at the end of the record reviews to reach a consensus on disagreements. All reports from the first three days of admission were combined into a single record. All extraneous reports (e.g. CT of the head) were eliminated.

Patient demographics were collected from the Admission, Discharge, and Transfer (ADT) record including date of birth and gender. Admission pattern was determined by examining the patient's ADT data for all previous visits to PUH in 2001. A visit was defined as the number of days from admission to discharge. Although a patient may have multiple visits throughout the course of a year, all analyses were conducted at visit level. The number of previous admissions was examined as both a continuous and categorical variable. Previous admissions were coded as a binary variable using one week as the cut point based on clinical plausibility and the natural history of IA.

For clinical labs, the first result after the time of admission was used. White blood cell count, hematocrit, platelet count, blood urea nitrogen, sodium, potassium, creatinine, bilirubin, aspartate aminotransferase, alanine aminotransferase, albumin, and calcium were examined. For hematocrit, sex-adjusted normal values were used (male 39-49, female 35-45). Clinical laboratory results for anthrax patients were collected from the medical literature. In some cases,

results were only described as ‘within normal limits,’ ‘normal admission laboratory results reported,’ or ‘normal levels reported’. More specific results were reported as ‘normal electrolytes reported’ or ‘normal serum chemistries.’ In situations where multiple laboratory results were available, such as Anthrax Case 6, the earliest was selected. All laboratory results are shown in **Appendix V**. Microbiological results for all blood and CSF cultures were retrieved for each patient visit.

Clinical characteristics of the 11 patients with inhalation anthrax in the 2001 bioterrorism event were abstracted from published case reports (160,279,280,281,282,283,284). All patients except for the Connecticut patient were described in the summary by Jernigan et al. In addition, six of the patients, including the Connecticut patient, were described in individual case reports. The clinical summaries from the case reports were extracted to a study form. The article itself was also attached to the form. Both were available to reviewers.

8.2 ANALYSIS

8.2.1 Analysis - Specific Aim 1

The analysis for this aim focused on describing the study population inclusion criteria and understanding the frequency and distribution of anthrax like illness over time to use as a baseline for the evaluation of a syndromic surveillance system for inhalation anthrax in an ED setting. Summary statistics described characteristics of the study cohort, including the frequency of each of four inclusion criteria for acute respiratory failure (blood gases, intubation, diagnosis,

and mechanical ventilation) and the inclusion criteria for radiologic findings (lymphadenopathy and mediastinal widening)

It is important to understand the frequency and distribution of flagged anthrax-like cases in the PUH ED over time. The analysis calculated the daily mean and standard deviation of anthrax like illness over time, single day minimums and maximums, changes in volume due to day of week, and week day versus weekend volume. No hypotheses were tested in Specific Aim 1.

8.2.2 Analysis - Specific Aim 2

Analysis for Specific Aim 2 focused on comparing the frequency of signs and symptoms between the historical inhalational anthrax cases and the identified anthrax-like subjects in the study population. The most discriminate clinical features were then used to build a decision tree for further classifying patients according to their clinical characteristics. Specific Aim 2 is formally stated in **Section 7.2.**

A complete listing of the analysis variables for Specific Aim 2 is found in **Table 17.** Radiologic and physical exam findings were analyzed as dichotomous variables. Any finding which reviewers marked as No, Uncertain, or Not Specified was considered negative for the finding of interest. Trauma as a cause for admission was grouped into four categories: those including motor vehicles, falls, gunshot wounds, and all other causes. A patient was considered positive for a significant medical history if any item on the Charlson index was present. Each "medical history" item was examined individually as a dichotomous variable. Microbiology results were grouped into three categories: gram-positive bacilli, gram-negative bacilli, gram-positive cocci. Previous admission was coded as positive or negative for having a previous visit

within one week and analyzed as a dichotomous variable. Laboratory results were analyzed as dichotomous variables using normal clinical ranges as cut points.

All data analysis was conducted using SAS version 9.2. (SAS Institute Inc., Carry, NC) Odds ratios with confidence intervals were calculated for all variables. (285) Confidence intervals were calculated according to the method of Simel. (286) Due to 100% prevalence of certain indicators (pleural effusions, consolidation, left lung pleural effusions, left lung consolidation), no odds ratio could be calculated, significance testing was done by Fishers exact test or chi square.

All variables found to have a lower confidence interval greater than 1.00 were retained for a decision tree analysis to further examine the most discriminate combination of clinical variables for use in a syndromic surveillance. The primary outcome for the tree was to determine presence of anthrax infection. All clinical predictors were input as binary categorical variables. For variables with missing data, CART chooses a surrogate variable with a distribution similar to the missing variable relative to the outcome. This means CART chooses a surrogate variable that is not explicitly included in decision rules in the tree but was used in the algorithm to predict the final variable set. A standard ten-fold cross validation scheme was used to determine the optimal tree by maximizing predictive accuracy while minimizing the number of terminal nodes ("complexity") in the tree. The tree with the lowest misclassification cost was chosen.

The tree was then used to score each patient encounter including syndromic and anthrax cases. Encounters were then plotted over time to illustrate the frequency and distribution of high and low probability cases. All decision tree analysis was conducted using Salford Predictive Model Builder v6.6 (Salford Systems, CA).

Table 17. Aim 2 Key Clinical Indicators

Consolidation?	**Pleural Effusions?**
Right Lung Consolidation	Right Lung Pleural Effusion
Right Upper Lung	Right Large
Right Middle Lung	Right Medium
Right Lower Lung	Right Small
Left Lung Consolidation	Left Lung Pleural Effusion
Left Upper Lung	Left Large
Left Middle Lung	Left Medium
Left Lower Lung	Left Small
Sign or Symptom^	
Cough	Chest Pain or Discomfort
Fever	Headache
Dyspnea	Confusion
Nausea or Vomiting	Abdominal Pain
Fatigue	Sore Throat
Myalgias	Rhinorrhea
Sweats	
Medical History Item	
Significant medical history?	Dementia
Chronic pulmonary disease	Peptic ulcer disease
Cereberovascular disease	Mild liver disease
Renal disease	Hemiplegia or paraplegia
Peripheral vascular disease	Any malignancy
Rheumatologic disease	Moderate or severe liver disease
Diabetes	Metastatic solid tumor
Myocardial Infarction	AIDS
Congestive Heart Failure	
Laboratory study	
WBC Count, 10^9 cells/L	Creatinine, mg/dL
Hematocrit, %	Bilirubin, mg/dL
Platelet count, x 10^9 platelets/L	Aspartate aminotransferase, U/L
Blood urea nitrogen, mg/dL	Alanine aminotransferase, U/L
Sodium, mM	Albumin, g/dL
Potassium, mM	Calcium, mg/dL
Microbiology result	
Gram Negative Rod	Gram Positive Cocci
Gram Positive Rod	

8.2.3 Hypotheses Aim 2

In order to evaluate the potential of emergency department data for a syndromic surveillance case definition of inhalation anthrax, it is important to understand the clinical picture of the patients presenting in the ED. The overall alternate hypothesis for Aim 2 was that there exist significant clinical differences between the characteristics of the 2001 bioterrorism anthrax patients and the characteristics of the identified syndromic patients at PUH. Five distinct clinical sub-analyses were conducted. Hypotheses for each analysis are given below.

Signs and symptoms**:** Myalgias, fatigue, nausea, sweats, cough, fever, headache, dyspnea, confusion, chest pain, rhinorrhea, and abdominal pain are predictive of anthrax. Rhinorrhea and sore throat should not be protective, as reported in the literature, due to low prevalence of seasonal respiratory conditions among syndromic patients.

Medical history: Patients may exhibit anthrax-like illness due to a co-morbid condition. Items from the Charlson Index were examined due to their prevalence and severity. A simple test for any Charlson Index item should differentiate syndromic patients from anthrax patients. Examining each co-morbid condition on the Charlson Index, items related to serious chronic respiratory complications should differentiate syndromic patients from anthrax patients.

Radiologic findings: Pleural effusions and/or consolidation were found in all 11 anthrax cases. These findings should occur with relatively lower frequency in the syndromic group. Anthrax patients should have a significantly higher proportion of pleural effusions and consolidation on chest radiograph.

Visit Pattern: Anthrax is a biphasic disease. Patients may be more likely to be seen twice in one week – once in the prodromal phase, once in the fulminate phase. Anthrax patients ought

to have a significantly higher proportion of patients with a visit in the week prior to their admission.

Clinical Labs: Anthrax patients have a distinct laboratory profile. Anthrax patients should have significantly high AST, high ALT, low sodium, high BUN, high hematocrit, high bilurubin low calcium, and low albumin laboratory values as demonstrated in the literature. Other labs may be protective such as low potassium, high creatinine lab values given their low prevalence in recent anthrax cases.

8.2.4 Analysis - Specific Aim 3

Specific Aim 3 focuses on constructing a set of realistic outbreak data sets to test the accuracy and timeliness of each detection method. While this aim does not test a hypothesis, it outlines and provides understanding to the size, length and distribution of outbreaks in a potential syndromic surveillance system, and illustrates their possible detection in an ED-based system. Specific Aim 3 is formally stated in **Section 7.3.**

Creating a "synthetic" or "simulated' outbreak is a technique which adds excess case counts to an existing time series of surveillance data. The technique employed in this study is similar to simulated outbreaks created for the studies by Jackson, Murphy and Zhu, reviewed in the **Analytical methods** section on beginning on **page 69**.

However, instead of creating large numbers of hypothetical scenarios corresponding to typical outbreaks seen in the community, a very specific focus on the epidemiologic patterns of the 2001 anthrax attack was maintained. The primary epidemiologic reference for the attack was "Investigation of bioterrorism-related anthrax, United States, 2001: epidemiologic findings". (271)

8.2.5 Outbreak parameters

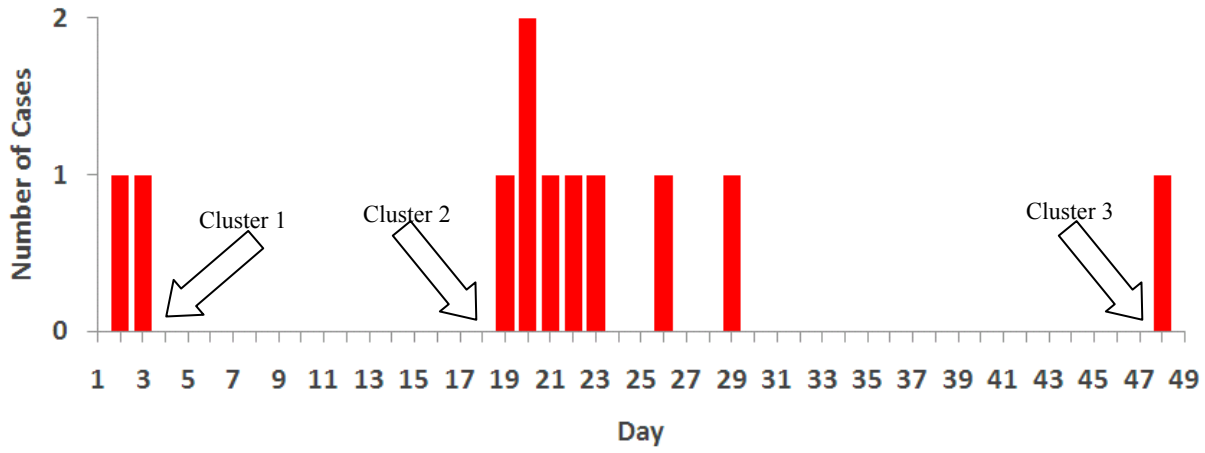


Figure 16. 2001 Inhalation Anthrax Attack

The 2001 attack, as described by Jernigan is plotted in **Figure 16.** The entire outbreak lasted 47 days, with the first patient hospital visit on October 1st and the last on November 17th. The outbreak consisted of 11 cases, with a single day maximum of two cases. The outbreak has three major disease clusters. Each cluster corresponds to a distinct exposure due to anthrax letters sent to three offices in Florida, Washington, D.C., and New York. From this source data, six outbreak simulations were created for the 2001 PUH ED time series.

The first simulation created in this specific aim superimposed the excess counts from the 2001 anthrax attack to the PUH time series exactly as they occurred in time. As shown in the timeline in **Figure 16,** one case was added on day 1 (October 1st), one case on day 2 (October 2nd), and so forth.

The second simulation created was similar to the first simulation in that the excess counts from the 2001 anthrax attack were added to the PUH time series exactly as they occurred in time. However, the start date was varied. This was done in order to remove bias created by the seasonality, healthcare utilization, or most importantly, Sept 11th attacks.

The third, fourth, and fifth simulations relied on the three disease clusters within the 2001 attack. These are labeled in **Figure 16.** The first cluster ("Cluster 1") consisted of 2 cases over a 2 day period. The second cluster ("Cluster 2") consisted of 8 cases over 11 day period. The third cluster ("Cluster 3") consisted of a single case. These were chosen to recreate possible anthrax letter mailings based on the incidence from 2001. Each simulation chose a start date at random. Although there was no way to vary the distribution of Cluster 1 or Cluster 3, a random distribution of the case counts in Cluster 2 was used over an 11 day period with a 2 case single-day maximum.

The sixth outbreak scenario randomly distributed the 11 inhalation cases over a 48 day period ("All clusters"). To maintain the historical limits from 2001, a single day case count maximum of 2 cases was used. This scenario provided the most variability in outbreak simulations give the very high number of combinations of start date and distribution.

For each cluster type, a custom SAS program was written to generate the appropriate data sets. A dataset to provide the daily number of syndromic visits was created. Each day of 2001 was numbered from 1 to 365 corresponding to admission dates from 1/1/2001 to 12/31/2001. The number of syndromic patient visits was recorded for each day. The number of daily historical anthrax cases was also recorded to be used with the 2001 Cluster and All Clusters scenarios.

Five outbreak sets were created based on the scenarios described by Jernigan. Each set was created using SAS 9.2 software. Before data simulations could occur, it was necessary to prepare the underlying time series. First a data set was prepared for the 2001 PUH admissions. This data set consisted of the number of syndromic anthrax cases for each day of the year, numbered 1-365, which corresponded to the dates of January 1st – December 31st. This data set provided the daily number of syndromic cases for the 'baseline' population and was derived from Specific Aim 1.

For each of the simulations, there were three major steps: randomly distribute excess syndromic cases for the appropriate time frame, create the correct number of outbreaks, and then run the three analytical methods on each outbreak to determine if the outbreak was detected.

The first step was to randomly distribute excess syndromic cases for the appropriate time frame. This step begins by first knowing the number of cases, the duration of the outbreak, the start date of the outbreak, and the maximum number of cases, if any, for any one single day. All of this information was gathered from the article by Jernigan et al and is detailed in the section **8.2.5 Outbreak parameters**. Start date was determined by random number generation with only numbers greater than 30 and less than 365 minus the duration of the outbreak retained. Once a start date was established the distribution of the cases was determined.

For scenarios '2001 Outbreak', Cluster 1, and Cluster 3 no randomization was required because the distribution was set. Only a start date was chosen. However for 'Cluster 2' and 'All Clusters' randomization was used to distribute the cases across the duration of the outbreak. This process assigned each day of the outbreak, 11 days for Cluster 2 and 48 days for All Clusters, a random number. This was done for ten thousand uniquely identified outbreaks. The outbreaks were then sorted by ID number and then random number. Depending on the number of cases for

the outbreak, 1 or 2 cases were then added for each day of the outbreak until the total number of cases was reached. The outbreaks were then resorted back to their original order by date. This is illustrated for Cluster 2 in **Table 18**.

Table 18. Randomly Distribute Cases

Generate correct number of days	**Randomize**		**Assign cases accumulating to predetermined total**		**Re-sort**	
Day	Random No.	Day	Day	Cases	Day	Cases
1	0.0135	9	9	1	1	
2	0.2009	7	7	2	2	2
3	0.2670	10	10	1	3	
4	0.3833	5	5	1	4	1
5	0.3925	2	2	2	5	1
6	0.4423	4	4	1	6	
7	0.4565	11	11		7	2
8	0.4756	1	1		8	
9	0.5130	6	6		9	1
10	0.7595	3	3		10	1
11	0.9585	8	8		11	

Once the distribution of cases was determined, the excess cases were added to the baseline number of cases corresponding to the randomly selected start date. For example if the start date 50 was randomly chosen, Day 1 of the outbreak would be 50, Day 2 would be 51, etc. This process was repeated 10,000 times for all five outbreak scenarios until 50,000 total time series were generated, each one 365 days long with the appropriate number of excess cases added to it.

8.2.6 Analysis - Specific Aim 4

This aim determined the optimal statistical test for identifying inhalation anthrax outbreaks – significant departures from normal illness trends – as well as characterized which tests optimally perform under various combinations of outbreak size, duration, and distribution. This aim relied on results from Aim 1 where the baseline of the PUH ED was calculated. This aim also relied on the simulated data sets produced in Aim 3.

In public health surveillance, "outbreaks" are traditionally defined as an observed value being greater than an expected historical value for that same time period. This study used three detection methods to identify when identified visits may exceed the historical norm: the EARS C1 & C3 and the z-score method of Jackson.

The EARS C1 & C3 methods are featured in the package develop and maintained by the CDC BioSense program. (287) Also, the EARS C1 & C3 methods are supported and freely distributed by the CDC. (238,248,247,253) These statistical methods were developed based on a one-sided positive CUSUM (cumulative sum) calculation. The equation can be written as follows:

$$S_t=\max(0, S_{t-1} + ((X_t -(\mu_0 +k\sigma_{xt}))/\sigma_{xt}))$$

with a decision value of $S_t >2$, where X_t is the count, μ_o is the expected value, σ_{xt} is the standard deviation, k is the detectable shift from the mean, S_t is the current CUSUM calculation, and S_{t-1} is the previous CUSUM calculation. The length of the baseline was chosen as 14 days which was shown to be optimum in a recent study by Tokars. (249)

C3 is useful for identifying aberrations that gradually increase over short periods of time. The C3 uses a 14 day baseline with a two day offset and the threshold is based on a 3-day average run length of the one-sided positive CUSUM. The positive differences from the mean

for the past 3 days are then summed. The cumulative sum is then compared to the baseline period to determine its significance. C3 is designed to signal when consecutive days of high case counts occur since those counts would not be incorporated immediately into the baseline period after the initial flag. This is illustrated in **Figure 17.**

The baseline period for C1 is obtained from the previous 14 days immediately following the observed case counts. The threshold calculations for the C1 signal when observed case counts exceed 3 standard deviations above the baseline mean. This method differs from C3 in its handling of consecutive signal days. For C1, if a signal is noted on a particular day, the next day is less likely to produce a flag since the elevated count from the previous day will be immediately incorporated into the new baseline period. C1 is most useful for situations where signals can be monitored on a daily basis and accounted for quickly (i.e., within 24 hours). Therefore, being alerted to the same information the following day would be considered redundant and burdensome. This is illustrated in **Figure 17.**

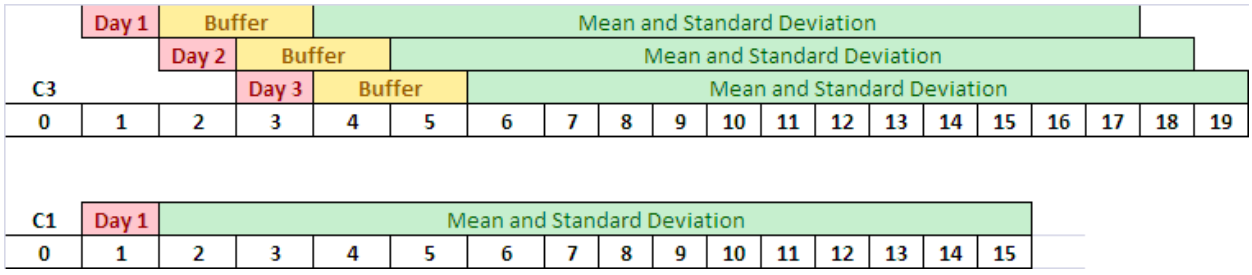


Figure 17. C1 and C3 Approaches

The WEWD Z score approach is featured in the ESSENCE package developed at Johns Hopkins University. The z-score approach differentiates between weekends and weekdays (WEWD) to calculate the difference of the observed day from the past 7 days. (238,268) This

adjustment is made to compensate for dramatically different healthcare utilization periods on the weekends. It is common that Sunday is the lowest volume day of the week thus leading to frequent Monday signals. The WEWD approach is illustrated in **Figure 18.** The mean and standard deviation of the prior 28 days are then used to calculate the z-score. When the z-score exceeds 2.00 (99% prediction interval), an alarm is sounded. The analysis showed no weekend effect in the baseline, therefore an unstratified z score was used.

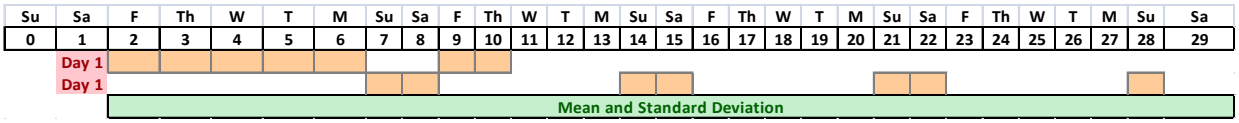


Figure 18. WEWD Z-Score Approach

After simulations are run for the three methods, each was evaluated according to accuracy, timeliness, and sensitivity. Accuracy measured the detection ability of the method. 'Detection' of an outbreak meant crossing the predefined threshold level during the time period containing the outbreak (i.e. z-score ≥ 2; cumulative sum ≥ 2). False alarms were defined as detection in the absence of an outbreak interval. The accuracy of each combination of baseline calculation and outbreak detection test was calculated by the number of outbreaks detected divided by the total number of outbreaks. Timeliness will be measured by the number of days between the outbreak start date and detection. Several hypotheses were tested according each of these evaluations.

Hypotheses - Aim 4

The overall hypothesis of Aim 4 was that syndromic surveillance for inhalation anthrax in an emergency department can provide accurate and timely identification of outbreaks.

1. Each of the three outbreak detection should detect the simulated 2001 inhalation anthrax outbreak.
2. The choice of baseline calculation improves the accuracy and timeliness of outbreak detection.
3. There exists a detection threshold which optimizes the balance between accurate outbreak identification and excessive false alarms.
4. Optimal performance of each anthrax outbreak detection will vary depending on characteristics of the anthrax outbreak simulation, including:
    a. Size: Total number of cases and daily maximums affect detection.
    b. Length: Duration of an outbreak will affect timeliness.
    c. Distribution: How cases cluster will determine optimal method.

9.0 RESULTS

This section presents the results of each of the four study aims. The primary goal of the first two Aims was to identify and describe a population which fit a syndromic surveillance case definition for inhalation anthrax with a focus on the Presbyterian University Hospital (PUH) Emergency Department (ED). The second aim evaluated several outbreak detection methods for identifying possible anthrax attacks.

9.1 AIM 1

9.1.1 Identify syndromic population

The syndromic case definition was defined as *any patient admitted to PUH from the ED with acute respiratory failure and radiological findings consistent with inhalation anthrax.* In 2001 there were approximately 16497 patient visits resulting in admission to PUH from the ED. **Table 19** shows that among those visits, 685 were intubated (ICD-9 96.04), 1198 required mechanical ventilation (ICD-9 96.7 or ICD-9 96.72) and 849 were given a diagnosis of acute respiratory failure (ICD-9 518.81). Of 3558 patient visits with arterial blood gas readings, 1126 encounters satisfied one of the two blood gas criteria: 706 had a PO2P < 60 and 689 with a PCO2P >= 50/PH<7.38. In all, 2478 patient visits were identified as meeting the criteria for acute respiratory distress.

Table 19. Inclusion Criteria

Dx & Procedures		No.	%
(n=16,497)	Intubation	685	4
	Ventilation	1,198	7
	Diagnosis	849	5
Blood gases			
(n=3,558)	PO2P <60	706	20
	PCO2 ≥ 50/PH <7.38	689	19
Radiology			
(n=461)	Any Radiologic Criteria	133	29
	Widened Mediastinum	93	20
	Lymphadenopathy	42	9

Radiology records were collected for the 461 of those patient visits that had at least one chest radiograph in the first 48 hours of their admission. Mediastinal widening was found in 93 visits and lymphadenopathy was found in 42 thus satisfying the syndromic case definition. A total of 134 of 16,497 (0.08%) total patient visits were included in the study. These 134 patient visits comprised the baseline population necessary to calculate the expected values in Aim 4.

Figure 19 shows each patient visit by admission date plotted over 2001 with the mean, 1x standard deviation (SD), and 2x SD with a 14 day moving average to smooth daily variations.

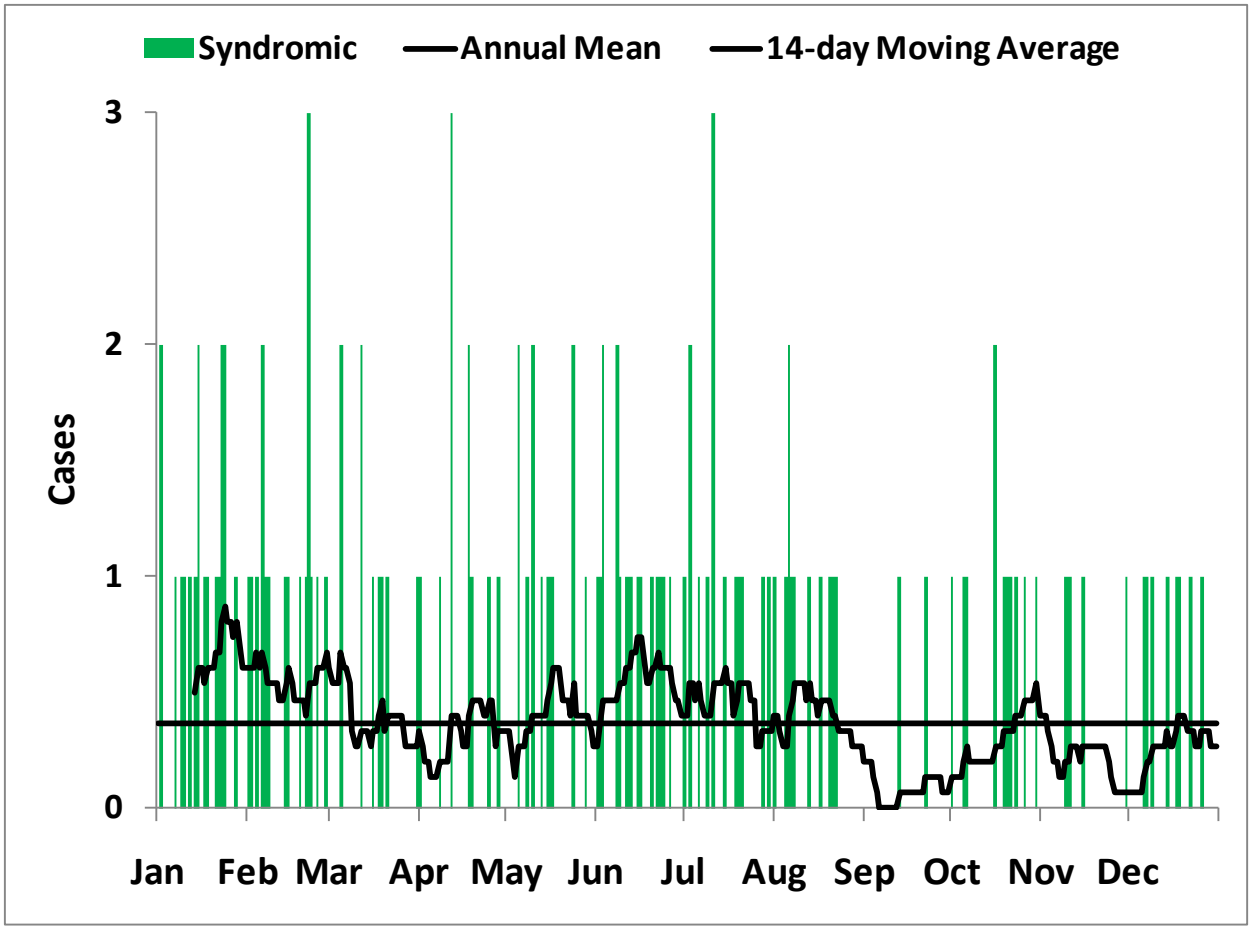


Figure 19. Baseline Population

Daily volume fluctuated from 0-3 cases per day. The mean number of daily syndromic visits was equal to 0.3 (SD=0.61). The mean percentage of total ED volume was equal to 0.81% (SD=1.4%). The maximum number of cases was equal to 3 on three occasions: Day 53, Day 102, and Day 192. The highest percentage of total ED volume was 8% and occurred on Day 154. The percentage of cases exceeded 6% on three occasions: Day 53, Day 102, and Day 192. Day-of-week did not affect volume with a weekday average count of 0.38 (0.81%) similar to weekend average count of 0.33 (0.84%).

9.2 AIM 2

The goal of the analysis for Aim 2 is to compare the 11 anthrax cases from the literature to the patients identified at PUH ED by applying a syndromic surveillance case definition. Subsequently, detailed clinical data is examined to evaluate the potential for an improved syndromic case definition for inhalation anthrax.

9.2.1 Identify Discriminating Factors

The first step in the analysis was to identify clinical characteristics which differentiate inhalation anthrax from other causes of acute respiratory failure with a widened mediastinum. Significant findings in this section formed the basis of a refined syndromic surveillance case definition resulting from decision tree analysis.

9.2.2 Demographic Summary

It is important to note in a demographic summary of the anthrax and syndromic patients that while all PUH patients were seen in Pennsylvania, anthrax patients were seen in six states across the Eastern seaboard: Maryland (3), Virginia (2), New York (1), New Jersey (2), Florida (2), and Connecticut (1). However, this geographic difference did not result in significant demographic differences. **Table 20** shows the number (No.) and percentage (%) of anthrax and syndromic patient visits by gender and race. Mean age in years is also given. **Table 20** shows syndromic patients were similar to the anthrax patients in both gender and age. Over 60% of each group was male. The syndromic group was predominantly white. There was no statistically significant difference in age between the two groups (p=0.51)

Table 20. Demographics

		Anthrax (n=11)		Syndromic (n=134)	
		No.	%	No.	%
Gender	**Male**	7	64	91	68
	Female	4	36	43	32
Race	**Black**	5	45	9	7
	White	3	27	115	86
	Asian	2	18	2	1
	Hispanic	1	9	0	0
	Other	0	0	8	6
Age	**Mean (yrs)**	60		56	

9.2.3 Power calculations

Based on this sample and a fixed number of records, a power analysis was conducted for significance testing portion of the research. Calculations were performed using the PS Power and Sample Size software developed by Dupont and Plummer at Vanderbilt University. (288) Given the fixed sample size of the study, the software provided the power to detect odds ratios at varying levels of prevalence for a Fisher's exact test at alpha equal to 0.05. **Figure 20** shows, for 11:134 matching, the power of detectable odds ratio (OR) from 2-25 at prevalence of 0.1 to 0.9. This level of matching is for analysis with all study subjects having complete records such as radiology reports. **Figure 21** shows, for 11:92 matching, the power of detectable odds ratio (OR) from 2-25 at prevalence of 0.1 to 0.9. This level of matching is for analysis with all study subjects having emergency department reports. The charts are color coded to differentiate analyses with the most power (green) from the least power (red). Results show that power of 80% in most analyses with a detectable OR > 8 and a prevalence < 40%.

	Prevalence								
OR	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
2	9%	13%	13%	12%	10%	7%			
3	24%	31%	32%	28%	22%	15%	8%		
4	39%	49%	49%	43%	33%	21%	10%		
5	52%	63%	62%	55%	42%	27%	12%		
6	63%	73%	72%	64%	50%	32%	14%		
7	71%	80%	79%	72%	57%	36%	15%		
8	78%	86%	85%	77%	62%	40%	16%		
9	83%	90%	89%	82%	67%	43%	17%		
10	87%	93%	92%	85%	71%	46%	18%		
15	96%	99%	98%	95%	83%	56%	20%		
20	99%	100%	99%	98%	89%	62%	22%		
25	100%	100%	100%	99%	93%	67%	23%		

Figure 20. Power Calculations for Analysis Requiring Radiology Report Data

OR	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
2	9%	12%	13%	12%	10%	7%			
3	23%	30%	30%	27%	21%	14%	8%		
4	37%	46%	46%	41%	32%	21%	10%		
5	49%	60%	59%	52%	41%	26%	12%		
6	60%	70%	69%	62%	48%	31%	14%		
7	68%	78%	77%	69%	54%	35%	15%		
8	75%	84%	82%	75%	60%	38%	16%		
9	80%	88%	87%	79%	64%	41%	17%		
10	84%	91%	90%	83%	68%	44%	18%		
15	95%	98%	97%	93%	80%	53%	21%		
20	98%	100%	99%	97%	86%	59%	22%		
25	100%	100%	100%	98%	90%	63%	23%		

Figure 21. Power Calculations for Analysis Requiring Emergency Report Data

9.2.4 Signs and symptoms

ED reports were retrieved for 92 of 134 syndromic group patients. Odds ratios (OR) with 95% confidence intervals (LLCI, ULCI) were calculated for each ED report variable. **Table 21** shows all symptoms except abdominal pain and rhinorrhea to be statistically higher in the anthrax group than the syndromic group. Myalgias (muscle pain) were found to be most predictive, whereas cough, dyspnea, and fever were shown to be most common among anthrax patients.

Table 21. Signs and Symptoms

	Anthrax (n=11)		Syndromic (n=92)				
	Num	Pct	Num	Pct	OR	95% CI	
Cough	10	91	11	12	73.64	8.58	632.12
Dyspnea	9	82	25	27	12.06	2.44	59.71
Fever	9	82	7	8	54.64	9.83	303.66
Nausea or Vomiting	9	82	5	5	78.30	13.24	463.21
Fatigue	8	73	2	2	120.00	17.42	826.57
Myalgias	8	73	1	1	242.67	22.55	2610.95
Chest Pain or Discomfort	7	64	17	18	7.72	2.03	29.38
Sweats	7	64	1	1	159.25	15.61	1624.12
Confusion	5	45	9	10	7.69	1.95	30.30
Headache	5	45	2	2	37.50	5.98	235.24
Abdominal Pain	3	27	13	14	2.28	0.53	9.72
Sore Throat	2	18	1	1	20.22	1.67	245.43
Rhinorrhea	1	9	1	1	9.10	0.53	156.95

9.2.5 Previous admission

Given the biphasic nature of the anthrax illness, it is important to note differences in visit pattern between anthrax and syndromic patients. The analysis of admission pattern examined the possibility that anthrax patients more frequently visited the hospital twice in the same week. In the case of the 2001 attack, two anthrax patients were admitted, discharged and then later readmitted with severe respiratory findings. This visit pattern was less common among syndromic patients although not significantly so. **Table 22** summarizes the findings.

Table 22. Previous Admission for Anthrax and Syndromic Patient Populations

	Anthrax (n = 11)		**Syndromic (n = 134)**				
	No.	**%**	**No.**	**%**	**OR**	**95% CI**	
Prior visit within 1 week?	2	18	13	10	2.00	0.40	10.07

9.2.6 Trauma

Of 94 patients meeting the syndromic case definition with emergency department records, 64 (69%) reported a traumatic cause of injury leading to admission. The leading cause of injury was motor vehicle accident (54%). No anthrax patient presented to the ED with trauma. Given the high prevalence of trauma among syndromic patients, it could serve as a useful rule out factor when conducting case investigations. **Table 23** summarizes the findings.

Table 23. Percentage of Trauma among Syndromic Patients

Description	No.	(%)
Motor vehicle accident	50	54
Fall	11	12
Gun shot wound	2	2
Ski accident	1	1

41 patients missing ED record

9.2.7 Medical history

Similar to trauma, medical history provides a clue as to the reason for admission. Because acute respiratory failure among anthrax patients was caused by the infectious disease process, this aim explored whether more syndromic patients would be admitted due to major underlying medical conditions. While there were a greater variety of underlying medical conditions among syndromic patients, there existed no significant difference. **Table 24** tabulates the results.

Table 24. Medical History

	Anthrax (n=11)		Syndromic (n=92)	
Medical history item	No.	%	No.	%
Cerebrovascular disease	2	18	4	4
Congestive heart failure			6	7
Chronic pulmonary disease	3	27	16	17
Dementia			3	3
Diabetes	1	9	4	4
Any malignancy			11	12
Myocardial infarction			1	1
Mild liver disease			2	2
Peripheral vascular disease	1	9	15	16
Renal disease	2	18	5	5
Rheumatologic disease	1	9	6	7

9.2.8 Radiologic findings – Consolidation

The radiology report provides primary evidence of inhalation anthrax by revealing the telltale sign of mediastinal widening. In addition, the radiology report can provide key

radiological findings indicative of inhalation anthrax such as the presence of consolidation or pleural effusions.

Table 25 shows consolidation in any location, right lung, right lower lung, and right middle lung were all found to be significantly higher in the anthrax group. Although, the point estimates appear to be higher in most significant indicators, the lower end of 95% CI (LLCI) were slightly above 1 in all 4 findings. Consolidation was found in 91% of anthrax patients with right lung being more common than left lung. The right lower lung was the most common lung region. The greatest significant difference between anthrax and syndromic patients was found in right lung consolidation (OR=13.10; 1.6, 105.3).

Table 25. Radiologic Findings – Consolidation

	Anthrax (n=11)		Syndromic (n=92)				
	Num	Pct	Num	Pct	OR	LLCI	ULCI
Consolidation?	11	100	74	55	*	*	*
Left Lung Consolidation	11	100	61	46	*	*	*
Left Lower Lung	6	55	46	34	2.30	0.66	7.93
Left Middle Lung	3	27	17	13	2.58	0.62	10.69
Left Upper Lung	1	9	23	17	0.48	0.06	3.96
Right Lung Consolidation	10	91	58	43	13.10	1.63	105.29
Right Lower Lung	8	73	46	34	5.10	1.29	20.16
Right Middle Lung	5	45	24	18	3.82	1.08	13.55
Right Upper Lung	2	18	32	24	0.71	0.15	3.45

** No odds ratio calculated, $p < 0.05$*

9.2.9 Radiologic findings – Pleural Effusions

Table 26 shows differences in the presence of pleural effusions (PE) were found to be more pronounced than with consolidation. Pleural effusions were found in 100% of anthrax

patients. No odds ratio was calculated but the p-value found to be less than 0.05. All anthrax patients had left lung pleural effusions. This finding was not so common among syndromic patients with only 55% having the finding. Pleural effusions in any location, left lung, and right lung were all found to be significant.

Table 26. Radiologic Findings – Pleural Effusions

	Anthrax (n=11)		Syndromic (n=92)				
	Num	**Pct**	**Num**	**Pct**	**OR**	**LLCI**	**ULCI**
Pleural Effusions?	11	100	74	55	*	*	*
Left Lung Pleural Effusion	11	100	61	46	*	*	*
Left Large	4	36	5	4	14.74	3.23	67.34
Left Medium	2	18	9	7	3.09	0.58	16.48
Left Small	5	45	42	31	1.83	0.53	6.32
Right Lung Pleural Effusion	10	91	58	43	13.10	1.63	105.29
Right Large	7	64	7	5	31.75	7.48	134.69
Right Medium	3	27	10	7	4.65	1.06	20.33
Right Small	0	0	33	25			

** No odds ratio calculated, p < 0.05*

9.2.10 Clinical labs

Clinical laboratory results can provide important indications of an infectious disease process like inhalation anthrax. Clinical laboratory results had varying availability for syndromic patients with sodium most available, and ALT/AST least available. Low albumin was the most prevalent anthrax finding. **Table 27** shows that among those patients with labs, low sodium and high hematocrit were the most discriminating features

Table 27. Clinical Laboratories

Laboratory study	Normal range	Anthrax No.	Anthrax %	Syndromic No.	Syndromic %	OR	95% CI	
WBC Count, 10^9 cells/L	**4.5-10.8**							
Low		0	0	3	2	~	~	~
High		4	36	73	58	0.4	0.1	1.5
Hematocrit, %	^^							
Low		0	0	105	70	~	~	~
High		4	36	3	2	28.2	5.3	151.0
Platelet count, x 10^9 platelets/L	**130-400**							
Low		2	18	16	15	1.3	0.3	6.6
High		0	0	9	8	~	~	~
Blood urea nitrogen, mg/dL	**10-20**							
Low		0	0	28	23	~	~	~
High		3	27	37	30	0.8	0.2	3.1
Sodium, mM	**136-145**							
Low		6	55	30	24	3.6	1.0	12.6
High		1	9	7	6	1.8	0.2	15.5
Potassium, mM	**3.5-5.0**							
Low		0	0	22	17	~	~	~
High		1	9	13	10	0.8	0.1	6.9
Creatinine, mg/dL	**<1.5**							
High		2	18	31	25	0.6	0.1	3.1
Bilirubin, mg/dL	**0.3-1.0**							
Low		2	18	2	6	4.1	0.5	33.3
High		4	36	15	45	0.7	0.2	2.7
Aspartate aminotransferase, U/L	**0-35**							
High		4	50	26	68	0.5	0.1	2.2
Alanine aminotransferase, U/L	**0-35**							
High		2	25	24	65	0.2	0.0	1.2
Albumin, g/dL	**3.5-5.5**							
Low		8	73	16	89	0.2	0.0	1.7
Calcium, mg/dL	**9.0-10.5**							
Low		4	50	66	92	0.1	0.0	0.5

^^ *Male 39-49, female 35-45.*

9.2.11 Decision tree

Decision trees analysis was conducted to identify the most predictive combination of clinical findings. The resulting tree could be useful for deciding which syndromic cases to investigate. **Table 28** shows all significant variables found to have a lower confidence interval greater than 1.0 that were retained for classification tree analysis. The analysis variables consist of nine findings from radiologic findings, 11 from signs and symptoms, and 2 laboratories. Presence of a gram positive bacillus and trauma were also included in the decision tree analysis.

Table 28. Summary of Variables Retained for CART Tree

			Anthrax (n=11)		Syndromic (n=134)				
Variable name	**Records**	**Missing**	**Number**	**Percent**	**Number**	**Percent**	**Odds ratio**	**LLCI**	**ULCI**
Right Lung Consolidation	145	0	10	91	58	43	13	2	105
Right Lower Lung	145	0	8	73	46	34	5	1.3	20
Right Middle Lung	145	0	5	45	24	18	4	1.1	14
Consolidation?	145	0	10	91	74	55	8	1.01	65
Right Large	145	0	7	64	7	5	32	7	135
Left Large	145	0	4	36	5	4	15	3	67
Right Lung Pleural Effusion	145	0	10	91	58	43	13	2	105
Right Medium	145	0	3	27	10	7	5	1.1	20
Pleural Effusions?	145	0	10	91	74	55	8	1.01	65
Myalgias	103	42	8	73	1	1	243	23	2611
Fatigue	103	42	8	73	2	2	120	17	827
Sweats	103	42	7	64	1	1	159	16	1624
Nausea or Vomiting	103	42	9	82	5	5	78	13	463
Fever	103	42	9	82	7	8	55	10	304
Cough	103	42	10	91	11	12	74	9	632
Headache	103	42	5	45	2	2	38	6	235
Dyspnea	103	42	9	82	25	27	12	2	60
Chest Pain or Discomfort	103	42	7	64	17	18	8	2	29
Confusion	103	42	5	45	9	10	8	2	30
Sore Throat	103	42	2	18	1	1	20	2	245
Abnormal CA	80	54	4	50	6	8	11	2	55
Low NA	137	8	6	55	30	24	4	1.1	13

Appendix U presents the detailed results of the CART analysis. **Figure 22** presents a graphical depiction of the optimal decision tree. The tree sorted all 145 patient encounters into 8 terminal nodes. Based on the composition of a terminal node, a probability for a patient encounter to be anthrax was calculated. For instance, 103 encounters did not have a cough. Of these 103, 102 also did not have fatigue. This terminal node is composed entirely of syndromic cases thus the chance of those encounters being anthrax is 0 out of 102, or 0%. The converse is true for the adjacent node. Only 1 visit did not have a cough but did have fatigue. The chance of anthrax within the node is 1 of 1, or 100%. Where 2 of 3 cases are anthrax the node is assigned a 66% chance. The results of this analysis could provide an algorithm to aid subsequent investigations of cases meeting the current case definition.

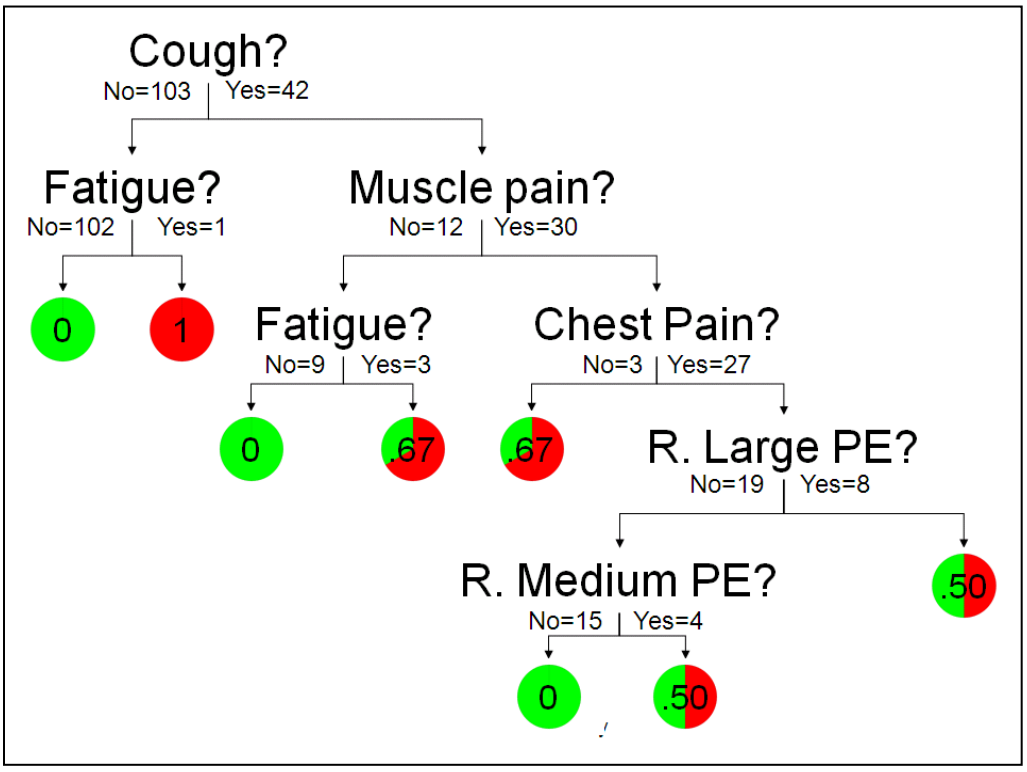


Figure 22. Decision Tree Results

Figure 23 illustrates the final decision tree. Each terminal node is colored to depict the possibility of anthrax: 0% chance of anthrax as green and 100% chance as red, the other four terminal nodes can be seen as yellow and orange or intermediate levels of risk.

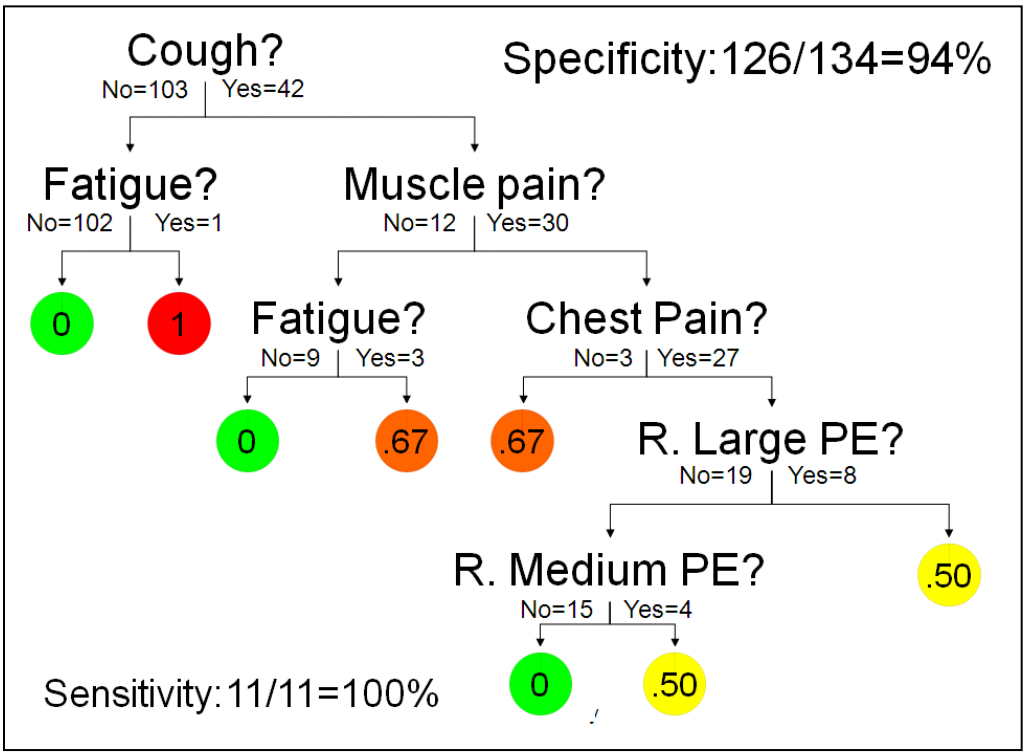


Figure 23. Decision Tree Results with Color Coding

Given that naturally occurring anthrax is extremely rare, monitoring for bioterrorism-related anthrax will detect almost exclusively false positives. The tree identified 126 of 134 cases correctly as not anthrax whereas 8 were incorrectly assigned to the anthrax group resulting in a specificity of 94%. The tree as a whole had a sensitivity of 100% which is to be expected with such a small case cohort.

Table 29 presents an index of importance as calculated by CART. To calculate a variable importance score, CART looks at the improvement measure attributable to each variable in its role as a either a primary or a surrogate splitter. The values of all these improvements are summed over each node and totaled, and are then scaled relative to the best performing variable. The variable with the greatest sum of improvements is scored the highest, and all other variables will have lower scores ranging downwards toward zero. (289)

Table 29. Variable Importance in CART Decision Tree

Variable	Score
Myalgias	100
Cough	91
Truama	90
Right PE	49
Dyspnea	44
Fatigue	41
Any PE	35
Nausea	35
Left PE	31
Fever	31
Sweats	21
Right Medium PE	13
Confusion	11
Chest pain	9
Right Lower Consolidation	6
Headache	4
Right Large PE	3
Any Consolidation	2
Right Consolidation	2
Left large PE	1

9.2.12 Decision Tree Results over Time

The intention of the decision tree analysis is to provide a daily tool for use by Infection Control practitioners to make the decision to investigate a cluster of cases or not. The interpretation of these results can best be examined if visualized over time as in **Figure 24**. Shown here are all anthrax cases and the 134 syndromic cases plotted by admission week and scored with the classification algorithm. The frequency ranges from 0-9 cases in any given week with an average of about 3 encounters. Shown below the scored encounters is the total frequency of patient encounters in the ED with a 7 day running proportion to illustrate any fluctuations in volume or trends in admission pattern. A typical week in the ED is about 300 visits. Six cases exceeded a probability of 0 in the first 36 weeks of the year. An implication for public health preparedness is that a busy ED in an urban setting could expect a syndromic case every couple days, while having to spend some time investigating a case about every six weeks.

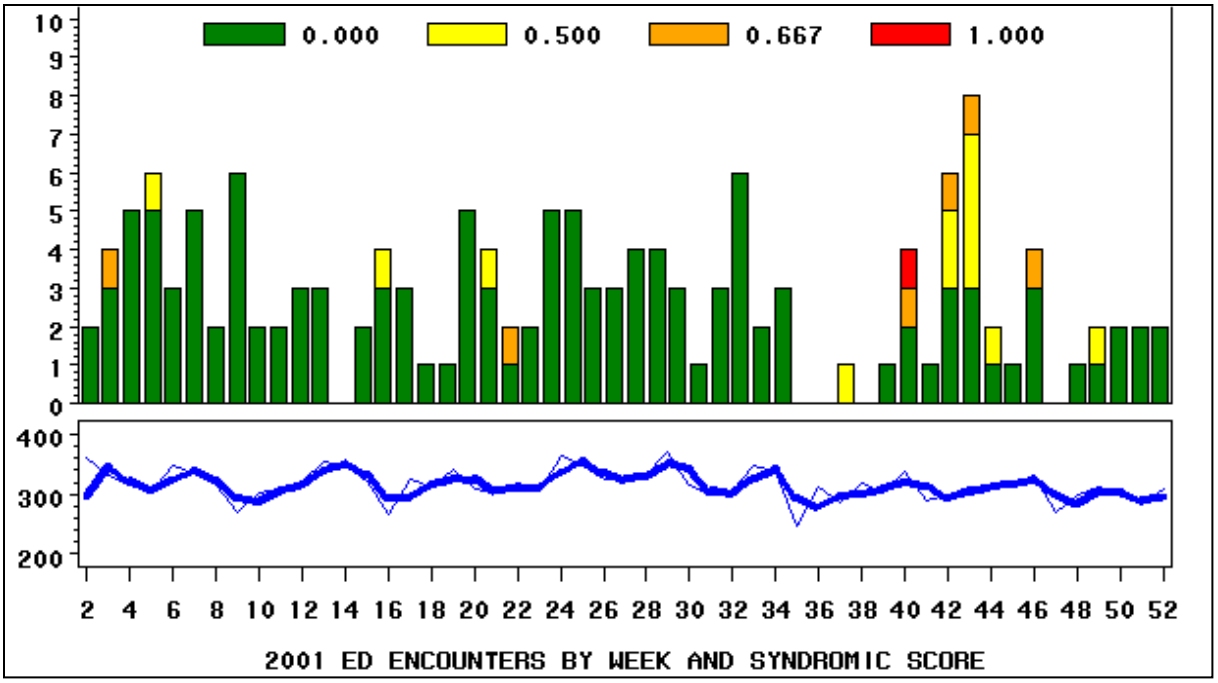


Figure 24. Decision Tree Results Plotted over Time

9.2.13 Focus on 2001 anthrax attack

Examining the events of October 2001, **Figure 25** illustrates that two patients meeting the syndromic case definition were admitted to the hospital on October 1st. If the algorithm were implemented, the orange case would be investigated for anthrax. In reality, the first case, Ernesto Blanco, stymied the clinical staff for three days. It is important that no anthrax cases would be missed if the lowest scoring cases ("green") were routinely excluded from investigation protocols.

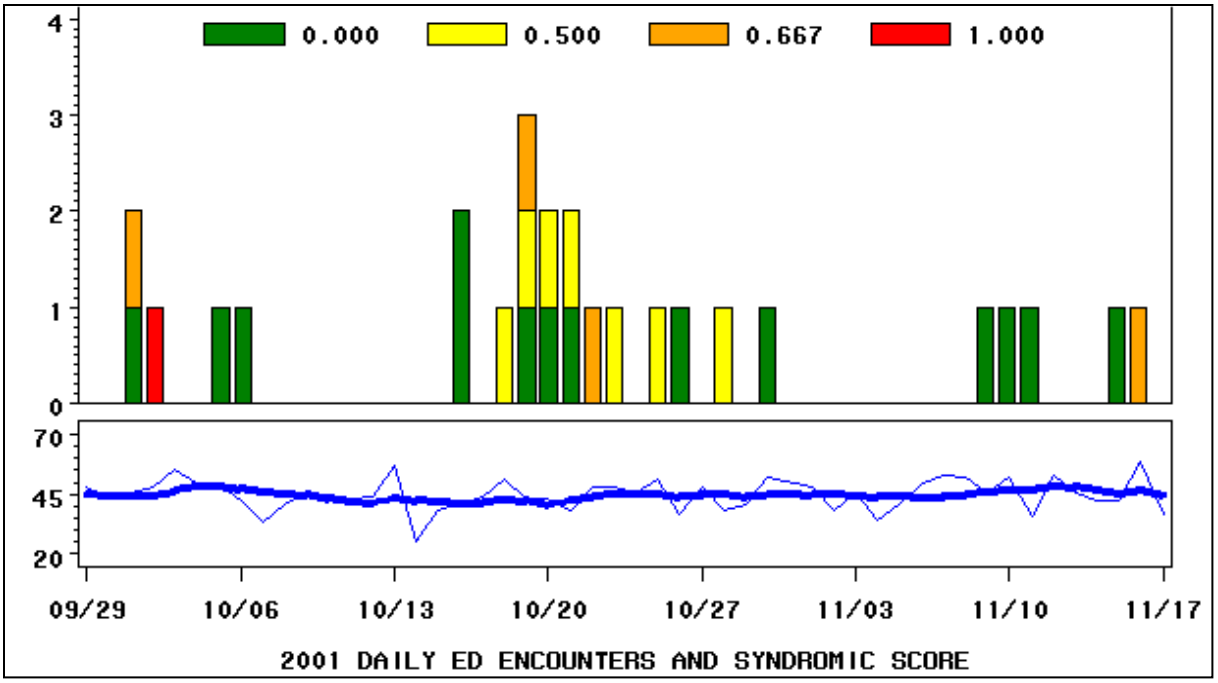


Figure 25. Decision Tree Results Focused on Anthrax Attack Period

To summarize Aim 2, a new way to look at syndromic cases of inhalation anthrax has been presented. Starting with fulminate symptoms and then using additional clinical data to narrow down a case cluster to only the most probable patients should decrease the time spent by outbreak investigators on annual basis.

9.3 AIM 3

The purpose of Aim 3 is to prepare analytical data sets for the analysis in Aim 4. Both Aim 3 and Aim 4 focus on a population-based approach to identifying outbreaks as opposed to a patient-based approach highlighted in Aim 1 and Aim 2. As described in **Section 8.2.4,** the 2001 anthrax outbreak provided 5 scenarios to test syndromic surveillance outbreak detection

approaches. Ten thousand outbreaks of predetermined size and length were generated for each scenario. **Figure 26** summarizes important parameters of the simulated outbreaks**.** "Minimum day" is uniformly set at 31 for all outbreaks to allow for sufficient ramp up time for baseline (30 days) calculations. "Minimum" and "Maximum" cases refer to the single day maximum or minimum as dictated by the individual scenario. For example, "Cluster 1" is a two-day, two case outbreak with a case occurring on each day. Therefore Minimum Case equals to 1 and Maximum Case equals to 1. In the "2001 Outbreak," "Cluster 2," and "All Clusters" scenarios there is greater variability of distribution allowing for 0 case days. All outbreaks were constrained to a maximum of two cases in a single day in accord with the 2001 anthrax attack maximum.

Description	Size	Frequency	Minimum Day	Maximum Day	Minimum Cases	Maximum Cases
2001 Outbreak	11	10,000	31	363	0	2
Cluster 1	2	10,000	31	365	1	1
Cluster 2	8	10,000	31	365	0	2
Cluster 3	1	10,000	31	365	1	1
All Clusters	11	10,000	31	365	0	2

Figure 26. Key Parameters for Simulated Outbreaks

Aim 1 showed daily counts of syndromic cases fluctuate throughout the year. In periods of less syndromic activity, outbreak detection methods are more likely to identify a significant increase. To avoid systematic bias each scenario start date was chosen at random. **Figure 27** shows the number of outbreaks per start date for all 60,000 simulations generated for this aim. **Figure 27** shows a fall in the number of outbreaks in the last 30 days of the year. This is because the 47 day outbreaks ("2001 Outbreak" & "All Clusters") must start before the 318th day of the year to finish by the 365th day. This decreases the volume by 20%. A similar fall off is seen at around 354 days for Cluster 2, an 11 day outbreak.

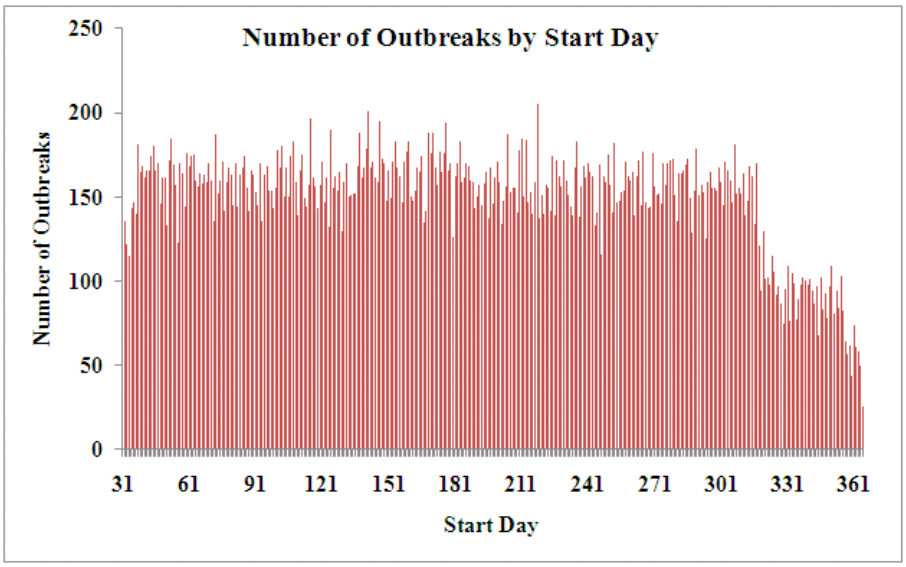


Figure 27. Distribution of Start Day for 50,000 Simulated Outbreaks

Two outbreak scenarios, All Clusters and Cluster 2, relied on randomization to distribute the excess cases across the outbreak interval. **Figure 28** shows the distribution of cases by percentage of all simulated cases for two outbreak types by day of outbreak. All simulated outbreaks begin with at least one case on Day 1. After the first day, both outbreak scenarios show fairly uniform distribution of cases for the remainder of the outbreak period.

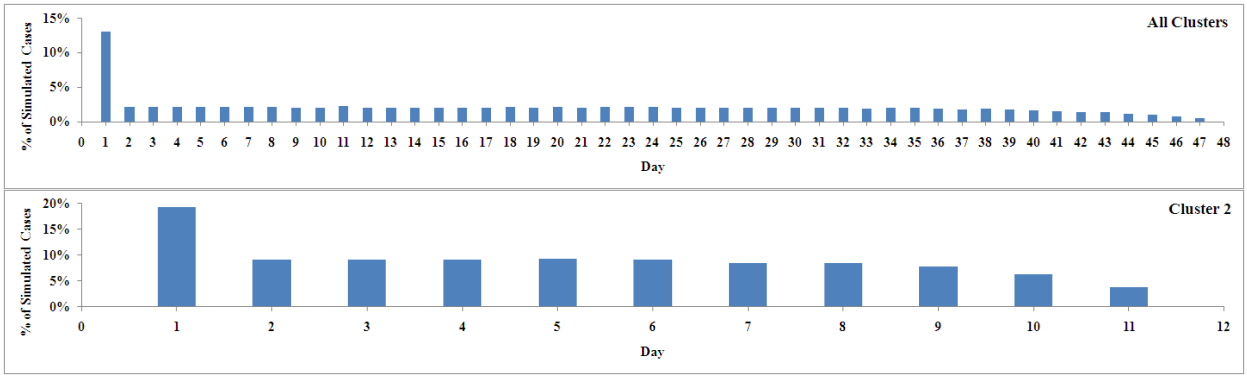


Figure 28. Distribution of Cases for Two Outbreak Scenarios

9.4 AIM 4

9.4.1 2001 Attack – Accuracy and Timeliness

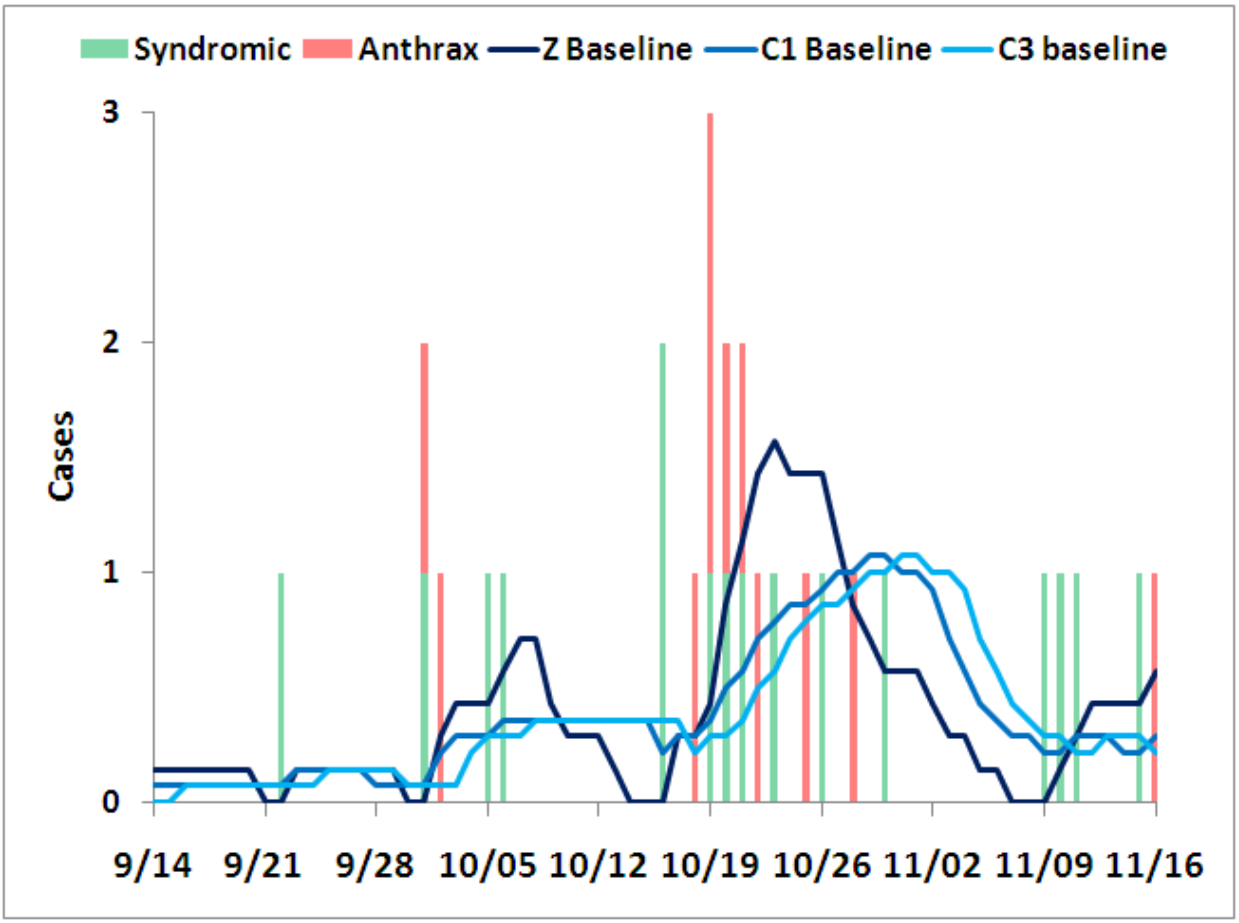


Figure 29. Baseline with Superimposed Anthrax Cases and Expected Values

The aim of this analysis was to determine the accuracy and timeliness of commonly used detection methods for inhalation anthrax outbreaks. Using daily ED data from PUH, the analysis provides a good example of how to simulate an anthrax attack using data on hand and how to conduct and evaluation a surveillance system when prospective outbreak data is not available.

The first step to understanding the accuracy and timeliness was to evaluate the performance of the three methods during the 2001 anthrax attack. **Figure 29** shows the 11 anthrax patient admissions (red) from the 2001 attack with the PUH syndromic patient visits (green) for the same time period. The daily expected value calculated for each of the three detection methods is also shown. Because outbreak detection methods signal depending on the difference of the observed value from the expected values, it is important to understand the behavior of each method as it relates to the 2001 attack. The z-method uses the 7 days immediately preceding the analysis day as the baseline to calculate the expected value, whereas C1 and C3 each use a 14 day baseline. The C3 method uses a 2 day buffer thus explaining the offset from C1 which does not have a buffer (See callout in **Figure 29**). Because the Z-score method uses the shortest baseline, it incorporates new cases immediately into the baseline, thus increasing its expectation. Conversely, C1 and C3 both use longer baselines with less volatility. In addition, the C3 method adds a two day buffer to its expected value calculation making it the last to incorporate new cases and the least volatile method.

Figure 30 illustrates the outbreak alarms generated by each detection method. Each day with a signal is denoted with a corresponding marker for the Z, C1, or C3 method.

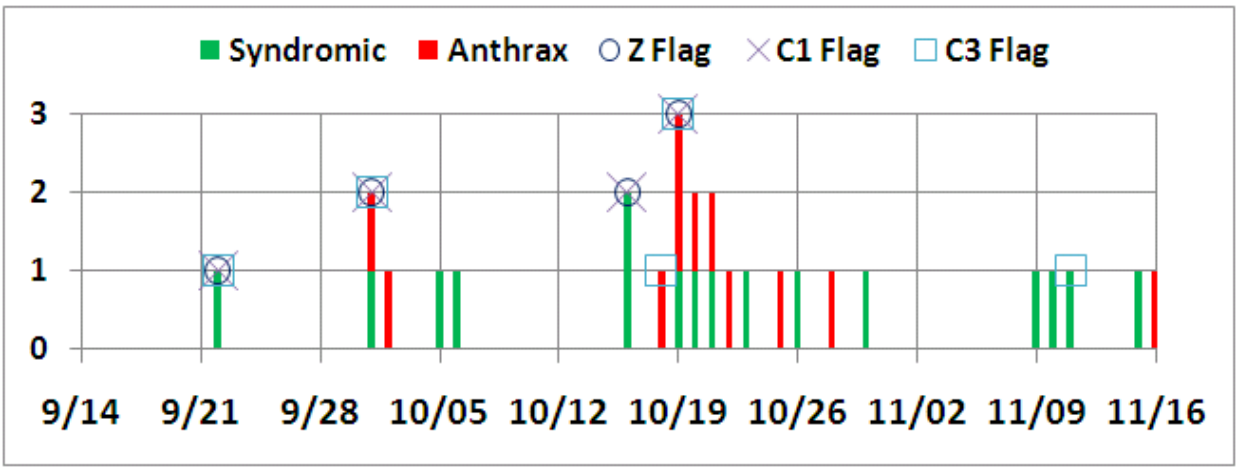


Figure 30. Anthrax Attack Period with Flags for Significant Increases in Syndromic Cases

At the time of the first anthrax case, October 1st, all three methods were expecting extremely low numbers of cases: Z (0.00), C1 (0.07) and C3 (0.07). At the time of Cluster 2, October 18th, Z (0.29) and C1 (0.29) had incorporated the two benign syndromic cases from October 16th into their baseline whereas C3 remained slightly lower (0.21) resulting in a signal. By October 19th, all three methods crossed their signal threshold. Throughout the attack period, 6 signal days occurred. **Figure 31**shows the signal values for each method for the same period.

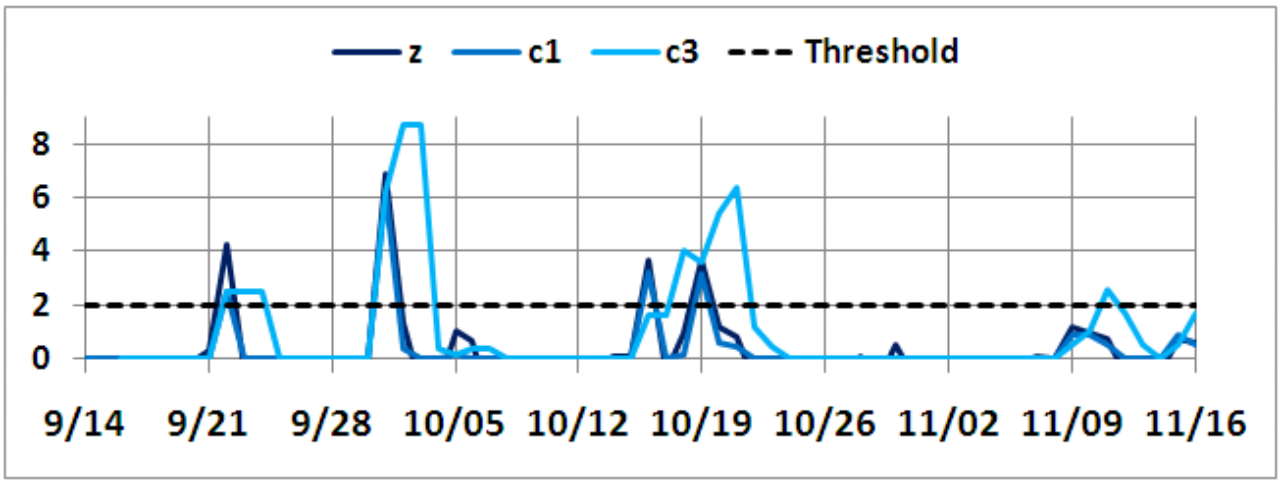


Figure 31. Signal Values for Outbreak Period

An alarm occurs when the signal threshold is exceeded. The broken line denotes that for all three methods the signal threshold was set at 2. Of the three major anthrax clusters, each of the methods detected the first two clusters. However, no method detected the third cluster.

To better understand the dynamics of the last anthrax case, Cluster 3, **Table 30** shows the relative strength of signal for each of the outbreak days.

Table 30. Anthrax Attack Period Signals Details

				Z			C1			C3		
Date	Anthrax	Syndromic	Total	Baseline	Signal	p	C1 Baseline	Signal	p	C3 Baseline	Signal	p
10/01	1	1	2	0.00	**6.87**	**0.00**	0.07	6.22	0.00	0.07	6.22	0.00
10/18	1	0	1	0.29	0.99	0.16	0.29	0.17	0.43	0.21	**4.04**	**0.00**
10/19	2	1	3	0.43	**3.67**	**0.00**	0.36	3.17	0.00	0.29	3.61	0.00
11/16[3]	1	0	1	0.57	0.55	0.29	0.29	0.52	0.30	0.21	**1.69**	**0.05**

In the days preceding Cluster 3, the baseline was affected by the three successive syndromic visits from 11/9-11/11. However, on 11/15 a single case was incorporated into the

baseline of both Z and C1. Because of the buffer on C3, the case did not influence the C3 expected value quite as high as Z and C1. Although no method picked up the 11/16 outbreak, C3 was the closest its signaling threshold with a value of 1.69 and a *p value* of 0.05.

9.4.2 Accuracy

To better understand the quality of each detection method, accuracy was examined across five outbreak scenarios. Accuracy is measured by the number of outbreaks detected during the outbreak interval out of a possible 10,000 simulated outbreaks. **Table 31** shows the accuracy of each of the three outbreak detection methods the 5 outbreak scenarios where "Detected" is an outbreak detected by *any* of the three methods.

Table 31. Accuracy of Three Methods on Simulated Outbreaks

Description	Length	Size	Number	Detected	Z	C1	C3
2001 Attack	47	11	10,000	10,000	9,927	9,647	10,000
Cluster 1	1	2	10,000	5,944	4,871	2,941	4,187
Cluster 2	11	8	10,000	9,676	9,230	7,285	9,244
Cluster 3	1	1	10,000	4,338	3,501	1,911	2,425
All Clusters	47	11	10,000	9,965	9,891	9,030	9,642

Overall, the three methods performed best on the larger outbreak scenarios. For the "2001 Attack" and "All Clusters", nearly every outbreak was detected by one of the three methods. This is in part because of the size of the outbreak and the length of the outbreak which gives the method a longer period of time to signal. Conversely, "Cluster 3" which is a single case outbreak showed the worst performance. In this scenario, the outbreak is small and must be detected in a single day. To examine the three methods individually, there is clearly a superior approach. The

Z method outperformed C1 and C3 in every scenario except the 2001 Attack. The poorest performance was seen in C1 especially in the single case outbreak.

9.4.3 Timeliness

A key indication of the quality of a surveillance system is how quickly outbreaks are detected. **Section 9.4.2** demonstrated nearly identical accuracy for both the Z-score and C3 method across a variety of scenarios. However, syndromic surveillance systems require not only accurate but timely outbreak detection to be most effective. The section illustrates clear differences in the two methods.

A direct comparison of methods is possible by identifying the first outbreak signal (or signals in the case of a tie.) **Table 32** presents the number (No.) and percent (%) of outbreaks detected first by outbreak scenario for each method. The Z method detected outbreaks first 90% of the time which is clearly superior to the performance of C1 (67%) and C3 (70%).

Table 32. Percent of Outbreaks Detected on Day 1 of Outbreak by Method

		Z			C1			C3		
Description	Outbreaks	Detected	No.	%	Detected	No.	%	Detected	No.	%
2001 Attack	10,000	9,927	8,356	84%	9,647	4,893	51%	10,000	5,777	58%
Cluster 1	10,000	4,871	4,746	97%	2,941	2,612	89%	4,187	3,439	82%
Cluster 2	10,000	9,230	8,446	92%	7,285	5,719	79%	9,244	6,847	74%
Cluster 3	10,000	3,501	3,501	100%	1,911	1,911	100%	2,425	2,425	100%
All Clusters	10,000	9,891	8,732	88%	9,030	5,595	62%	9,642	6,521	68%
	50,000	37,420	33,781	90%	30,814	20,730	67%	35,498	25,009	70%

Signaling first is a different quality than signaling on the first day of the outbreak. An examination of signal day still shows the performance of the Z method as superior. However, the timeliness dips as signals on the first day are highlighted. **Figure 32** shows the percentage of total outbreaks by signal date for the Cluster 1 type outbreaks for each outbreak detection method. Although the Z method demonstrates the timeliest detection, only 35% of the outbreaks are detected on the first day.

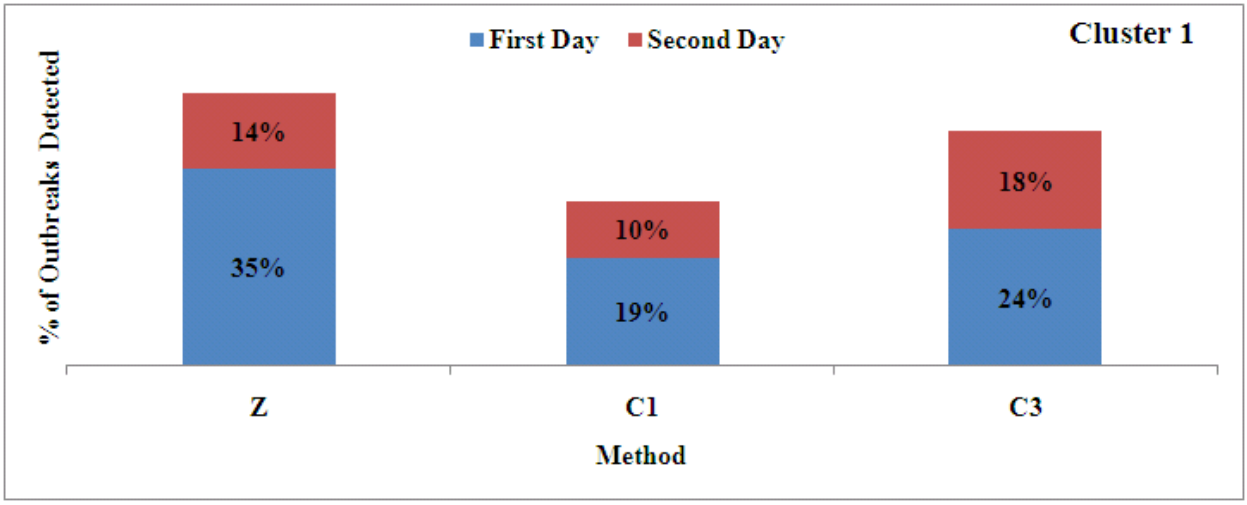
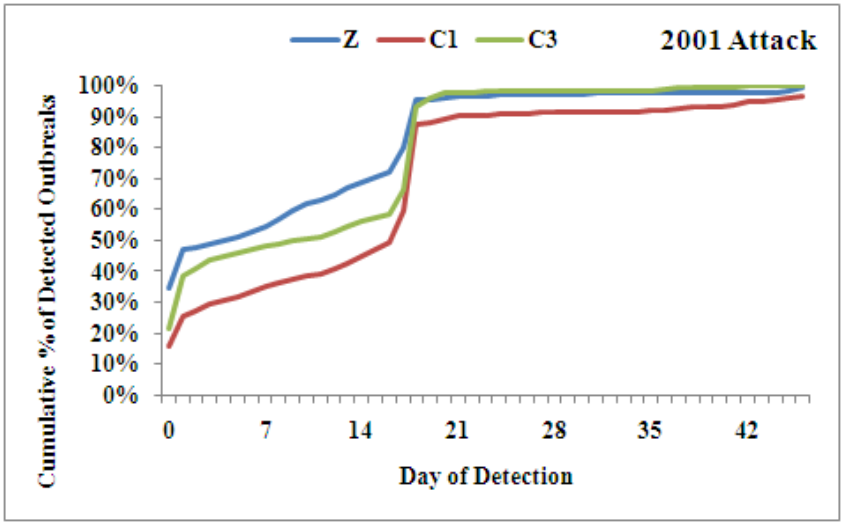
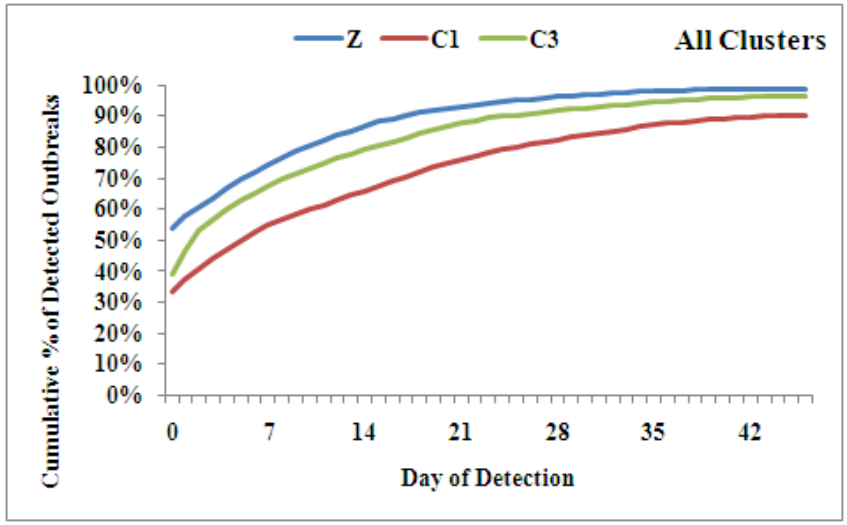


Figure 32. Signal Day for Cluster 1 Outbreak Type

Figure 33 shows the cumulative percent of outbreaks detected by signal day for the "2001 Attack", "Cluster 2" and "All Clusters" outbreak types. As the day of detection increases, the cumulative percentage of outbreaks increases. The 2001 Attack signal dates are clearly defined by the distribution of the anthrax cases over the outbreak period. Moreover, the Z method shows a higher cumulative percentage across all three scenarios.





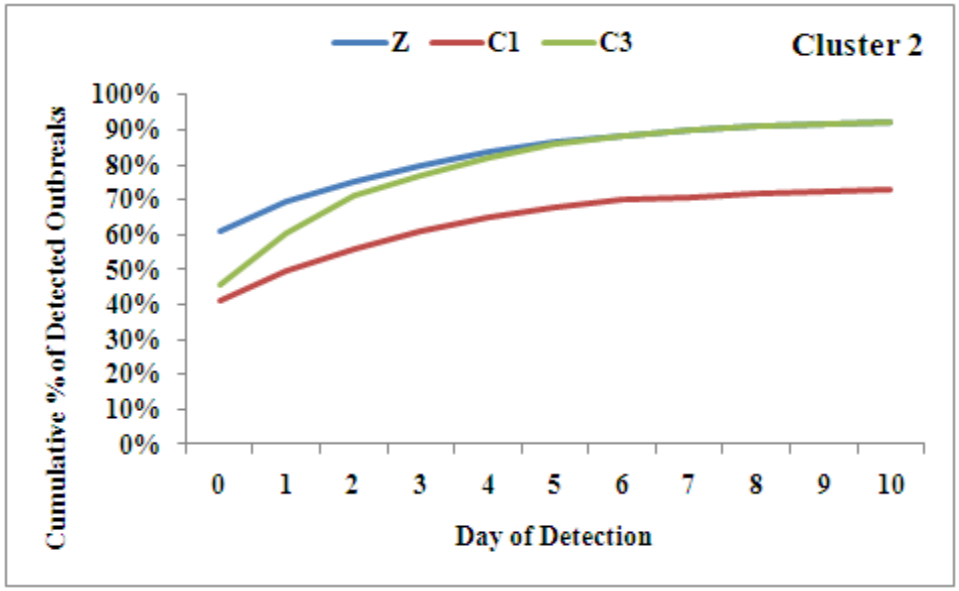


Figure 33. Signal Day for 2001 Attack, All Clusters, and Cluster 2 Outbreak Types

9.4.4 False alarms

When a surveillance system sounds an alarm in the absence of an outbreak, it is considered a false alarm. To truly understand the usefulness of a surveillance system, the number of false alarms throughout the course of a year must be taken into account because statistically significant increases do occur by chance. **Figure 34** presents the daily number of syndromic cases with the alarm flags for the 2001 PUH ED syndromic baseline. From January to August, most days with 2 or more cases generated an alarm by at least one method. As the syndromic case volume decreased in the later part of 2001, more days with single cases caused false alarms. The breakdown of false alarms (No.) is as follows: Z (20), C1 (12), and C3 (22).

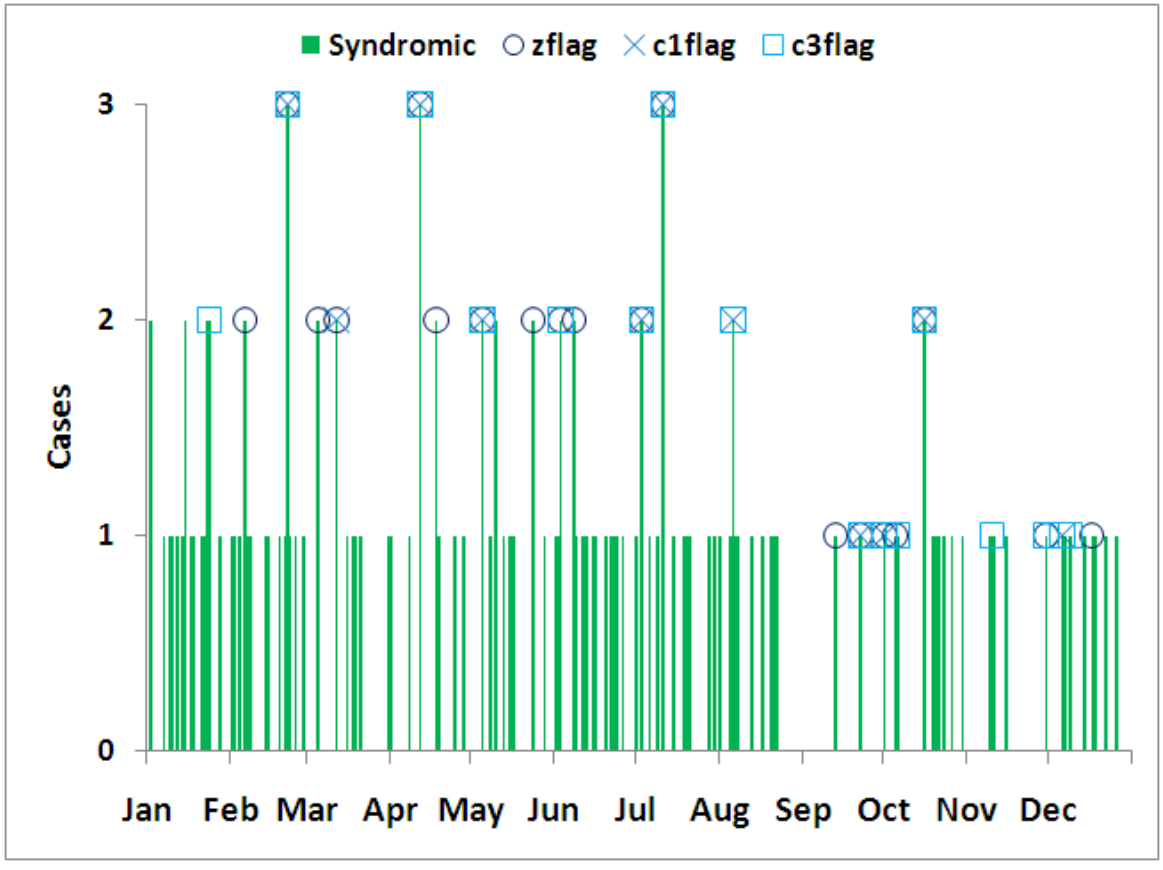


Figure 34. Signal Flags

There were 8 overlapping alarms during 2001 meaning all three methods falsely signaled on the same day. It is probably more important to understand the unique false alarm properties of the techniques. **Figure 35** shows that Z-score method falsely triggered 11 times, 8 of those singly.

		Z			C1			C3		
Date	Syndromic	Baseline	Signal	p	Baseline	Signal	p	Baseline	Signal	p
01/24	2	0.86	1.24		0.79	0.74		0.64	**2.29**	**0.01**
02/06	2	0.43	**2.05**	**0.02**	0.57	0.89		0.64	0.82	
03/05	2	0.14	**2.38**	**0.01**	0.57	0.68		0.57	0.68	
03/12	2	0.29	**2.20**	**0.01**	0.21	**2.08**	**0.02**	0.29	1.80	
04/18	2	0.43	**2.24**	**0.01**	0.29	1.08		0.29	1.08	
05/24	2	0.14	**2.90**	**0.00**	0.43	1.43		0.50	1.31	
06/03	2	0.43	**2.27**	**0.01**	0.36	1.59		0.21	**2.80**	**0.00**
06/08	2	0.57	**2.13**	**0.02**	0.36	1.59		0.50	0.97	
08/06	2	0.43	1.99		0.29	**2.66**	**0.00**	0.29	**3.18**	**0.00**
09/13	1	0.00	**2.83**	**0.00**	0.00	0.00		0.00	*	
10/05	1	0.14	**2.38**	**0.01**	0.14	1.36		0.14	1.36	
10/06	1	0.29	1.72		0.21	0.85		0.14	**2.72**	**0.00**
11/10	1	0.14	1.43		0.14	1.36		0.14	**2.72**	**0.00**
11/30	1	0.00	**2.70**	**0.00**	0.00	0.00		0.07	**2.47**	**0.01**
12/06	1	0.14	1.99		0.07	**2.47**	**0.01**	0.07	**2.47**	**0.01**
12/09	1	0.29	1.78		0.21	0.85		0.14	**2.72**	**0.00**
12/17	1	0.14	**2.10**	**0.02**	0.29	0.52		0.29	0.52	

Figure 35. Non-overlapping Signals, All Methods

The C1 method falsely signaled only three times, 1 of those alone. C3 falsely signaled 8 times, 4 of those unaccompanied. Although a small number of false alarms intuitively minimize the amount of unnecessary investigation, it also may signify less sensitive surveillance.

Table 33 presents the total number of false alarms across all 10,000 simulated outbreaks and the ratio of true signals to false alarms for the three outbreak types. Overall, despite

producing the least accurate and timely performance, C1 has the highest ratio of true outbreaks to false alarms. C1 produced an average of 10 (not shown) per surveillance year whereas Z (17) and C3 (15) produced more.

Table 33. Ratio of True Signals to False Alarms for 3 Detection Methods by Simulation Type

		Z			C1			C3		
Description	Outbreaks	Detected	False	Ratio	Detected	False	Ratio	Detected	False	Ratio
2001 Attack	10,000	9,927	161,654	0.06	9,647	93,673	0.10	10,000	134,919	0.07
Cluster 1	10,000	4,871	184,863	0.03	2,941	106,826	0.03	4,187	155,390	0.03
Cluster 2	10,000	9,230	175,682	0.05	7,285	102,748	0.07	9,244	149,483	0.06
Cluster 3	10,000	3,501	187,645	0.02	1,911	108,270	0.02	2,425	158,585	0.02
All Clusters	10,000	9,891	161,949	0.06	9,030	92,643	0.10	9,642	137,097	0.07
	50,000	37,420	871,793	0.04	30,814	504,160	0.06	35,498	735,474	0.05

10.0 DISCUSSION

This research examined the dynamics of establishing a syndromic surveillance system for anthrax in an ED setting. Anthrax is a significant public health issue because of its high case fatality rate and the potential for an outbreak to incite panic in the population. Traditional surveillance for anthrax is not well suited to identify anthrax outbreaks related to bioterrorism. This system is too slow in case identification and basing public health prevention efforts on its use would result in a large number of unnecessary deaths. Syndromic surveillance systems have been proposed as a solution to allow for quick case identification, and more rapid initiation of prevention strategies.

The goal of the research presented in this document is to examine the feasibility of a syndromic surveillance system for anthrax and its potential ability to identify the signs of an inhalation anthrax outbreak as early as possible. Key components investigated include an evaluation of the key signs and symptoms that would form a case definition for use in a syndromic surveillance system for anthrax, an evaluation of the accuracy of different detection methods in syndromic surveillance, and an evaluation of the timeliness of different detection methods in syndromic surveillance. The key findings of this research include the following: 1. A case definition based on the fulminate phase of anthrax, as opposed to the prodrome, significantly decreases the number of potential case investigations 2. Decision tree based clinical algorithms may be applied to the clinical findings of patients to further decrease the number of case investigations. 3. Potential anthrax outbreaks may be identified in an accurate and timely manner with a minimum number of false alarms using well-known outbreak detection methods.

10.1 SYNDROMIC CASE DETECTION

Aim 1 and Aim 2 focused on identifying patients resembling inhalation anthrax and then used clinical characteristics of those patients to further discriminate inhalation anthrax from other causes of acute respiratory failure with a widened mediastinum. Aim 1 and Aim 2 are formally stated in **Section 7.1** and **Section 7.2.**

These aims hold public health significance because of the deadly nature of the disease and the potential for an anthrax attack to incite panic in the general population. Specifically for inhalation anthrax, the goal of this research is to identify the first case of inhalation anthrax in an Emergency Department population or identify the first signs of an inhalation anthrax outbreak as early as possible. The key findings of the research represent important first steps to reaching these goals.

Aim 1 found that a syndromic surveillance case definition focused on fulminate phase anthrax findings like acute respiratory failure (ARF) and widened mediastinum identified about 1% of the PUH ED population. The billing code for mechanical ventilation (ICD9- 97.1/97.2) identified the highest number of ARF cases (10%). This finding is consistent with a multicenter Scandinavian study of acute respiratory failure identifying about 9% of ICU admissions. (290)

The time required to identify the various patients by the inclusion criteria varied substantially. The time required to develop and implement the various criteria for Aim 1 varied by data type. For facilities interested in using the case definition from his study, the time commitment may require consideration. For acute respiratory failure, all ICD criteria were straight forward. Either a patient's visit included the procedure or not. To develop these criteria, an attending Infectious Disease physician provided feedback as to what would be appropriate. Blood gas criteria are well established for acute respiratory failure and required very little time to

choose the exact source of an algorithm. However, the implementation of an arterial blood gas algorithm required data processing, programming time, and quality assurance to ensure the results were accurate.

The only way to identify mediastinal widening at the time of this study was to have radiologist's read full text reports. The training of the physicians, retrieval of the records, abstraction to a standard form, and tie breaking procedures was time consuming and the most expensive portion of the study. In addition the timing of data elements required to fulfill the case definition is not weighed. Each element is considered to be happening simultaneously. This is especially important in constructing the baseline for Aims 3 and 4, as admission date is used for each patient even though a chest x-ray or intubation may have occurred up to 48 hours after admission. Similarly the time to transcribe full text radiology reports or ED reports could also cause a lag.

Going forward, a less expensive review process based on structured data elements from an electronic health record may reduce the time and financial commitment required to implement this approach. Since 2000, when this study was first undertaken, federal initiatives to make electronic health record data available for syndromic surveillance are underway and set to be implemented in 2013. (291) Although syndromic surveillance for rare conditions is not sufficient cause to upgrade to an expensive electronic system, if a system is implemented for other reasons it would require few resources to capitalize on its capabilities to identify and manage a panel of patients across care settings.

The findings from Aim 2 differed in several areas from published literature seeking to identify inhalation anthrax cases. Myalgias were found to be the most significant clinical difference among ED report findings. Only one study, Kheunhert, examined the factor with the

difference being significant in ILI but not CAP populations. (155) Fatigue, in the same study, had no association with anthrax. Sweats were predictive in both CAP and ILI populations. (156) However, in each case, the magnitude of association was muted in the CAP, ILI comparisons as compared to the present study. This could be due in part to the choice of populations. In comparisons to ILI, CAP, or influenza, an underlying infectious disease process is occurring which leads to many similar symptoms to anthrax. However, a combination of widened mediastinum and ARF does not necessarily stem from a similar infectious disease process. In fact, 68% of patients with ED reports suffered a trauma leading to their admission. This represents a major strength of the present study to remove the underlying 'noise' of such similar patients from the baseline. It is not clear however that a trauma indicator could be reliably coded for syndromic surveillance. Rules based on ICD9 codes (Gun Shot Wound, Motor Vehicle Accident), presence of fractures, or intercranial hemorrhage are all possible indicators but beyond the scope of this research. As electronic systems develop, with template data entry prompting the user for presence of trauma, this indicator could become more readily available.

Comparison of the radiological findings between the anthrax and syndromic populations were consistent to findings from the literature. Even before clinical studies were conducted Jernigan highlighted that all 11 cases exhibited pleural effusions on chest radiograph. (6) These findings were echoed by Kyriacou, Kuehnert, and Hupert across several populations. (157) The present study shows the robustness of this finding given that the population was drawn from critically ill patients suffering ARF and a widened mediastinum.

In total, 134 cases were identified throughout 2001 as meeting the syndromic surveillance case definition for inhalation anthrax. To consider the practical implications of this work, it is important to understand the time and effort required to investigate these cases. The most obvious,

and expensive in terms of time, is for an infection control practitioner (ICP) to investigate every case as it happens, approximately 3 case investigations per week.

However, the CART analysis results provide a potentially more cost effective alternative to investigating every case. The CART tree, although limited by a small number of anthrax cases, provided a means to score each case as it occurs. Most cases (94% of syndromic cases) were scored 'lowest probability' (nearly zero). Applying an algorithm approach, which is a common practice in Emergency Departments, an ICP would only unnecessarily investigate 8 cases throughout the year.

A similar tree with similar objectives by Kyriacou found pleural effusions, confusion, and high hematocrit to be most predictive with a sensitivity of 100% and specificity of 98%. (159) In addition both Kuehnert and Hupert offer decision supports to predict anthrax infection with high sensitivity and specificity above 90%. These findings show that anthrax infection is distinct from most other candidate conditions. However, the underlying baseline chosen by other authors would lead to thousands of 'hits' per year as opposed to just over 100 by the current study.

Although an algorithmic approach clearly has advantages, there are several limitations to consider when implementing it for syndromic surveillance. Data preparation for the present study required the review of practicing ED physicians and radiologists reading full text reports. However, template data entry is more common today and often codes symptoms such as cough, fatigue, and muscle pain into ICD 9 which are easily input to an algorithm. In addition, algorithms should be updated regularly as patient mix changes. The expertise to re-run a program such as CART may not be present in a smaller health care facilities.

The results of Aim 1 and Aim 2 hold promise for the implementation of syndromic surveillance in an emergency department population especially for case detection. With such a system in place, the time necessary for creating a line list of patients resembling inhalation anthrax is substantially decreased. This would speed investigations if the threat of inhalation anthrax attack were heightened in the area.

As ambulatory healthcare settings migrate from the hospital setting to community providers, it is an open question whether emergency departments are still the appropriate setting to conduct this type of surveillance. Given the critical illness of the patients meeting the case definition, emergency departments are probably still most appropriate but in the foreseeable future changes to the health care process may necessitate a reexamination of settings for syndromic surveillance.

10.2 SYNDROMIC OUTBREAK DETECTION

Aim 3 and Aim 4 focused on identifying inhalation anthrax outbreaks using a syndromic surveillance approach. Different scenarios were simulated and then outbreak detection methods were applied to understand how outbreak size, distribution, length, and start date affect the accuracy, timeliness, and rate of false alarms of each technique. Aim3 and Aim 4 are formally stated in **Section 7.3** and **Section 7.4**.

These aims hold public health significance because of the syndromic surveillance has not focused on small, severe outbreaks. In particular no syndromic surveillance study has dealt with the detection of a small, deadly outbreak such as occurred in 2001, claiming the lives of 6 American citizens and hospitalizing 5 others. The results of the current study examine the 2001

attack in fine detail and answer the question "Would the 2001 attack be detected were it to occur at PUH?" The key findings of the research represent important first steps to reaching these goals.

Aim 3 identified three major disease clusters in the 2001 anthrax attack. In all 5 disease scenarios were identified to test the outbreak detection methods. For the two largest scenarios, the distribution of cases and start date was randomized. Although these simulations almost exhaustively present possible outbreak scenarios for testing, some limitations arise from certain design decisions. One limitation was due to the mean (0.37 cases/day) and standard deviation (0.61 cases) of the underlying time series. Because the mean was less than one case, it did not make sense to allow non-integer number of cases into the simulation. In addition, because the 2001 anthrax attack did not result in more than two patient admissions in one day, this limit was also used for the current study. Two excess cases in a single day represent an increase of 3.2 standard deviations of typical case volume.

Studies such as those conducted by Jackson et al. and Zhu et al. used up to five times the standard deviation to model case volume. (268,269) This was not justified in the current study where testing the *actual* cases counts was more important the *hypothetical* case counts. Although this simulation approach limits the generalizability of the findings for syndromic surveillance, it strengthens the findings for an outbreak specifically resembling the 2001 attack.

Aim 4 focused on identifying inhalation anthrax using 3 different outbreak detection methods in a variety of scenarios drawn from the 2001 anthrax attack. The first scenario superimposed the 2001 anthrax attack on to the 2001 PUH baseline identified in Aim 1. All three methods detected this outbreak on the first day. The success of each method may have been affected by an external factor. The baseline of syndromic cases was at an annual low from August 25th through the end of the year. At the time of the attack each method was forecasting

zero expected cases. This scarcity of syndromic activity does not appear to coincide with September 11th attack as it began two weeks prior. One way to better understand how the day of the anthrax attack, October 16th, affected the accuracy of the methods was to vary the start date of the attack. The "Cluster 1" simulation randomly chose start dates for the initial case cluster from the 2001 attack – 2 cases in 2 days. The outbreak detection performance declined once start date was varied from perfect detection across all three methods to 59% detection.

In terms of timeliness, the 2001 attack was detected on the first day by all three methods. When start date was randomized in "Cluster 1" simulations, only 20-30% of outbreaks were detected on the first day.

During this historically low period of syndromic activity, false alarms also increased. From September 13th to November 30th, every day with a syndromic case caused a false alarm – meaning the outbreak detection method registered a significant increase greater than 0.01 probability. This is not unexpected with syndromic surveillance. Timely systems tradeoff a certain number of false alarms for the assurance outbreaks are detected as quickly as possible.

Aim 4 uncovered trends in the minimum size of an outbreak able to be detected by the three methods. A clear trend is shown by looking at the accuracy of Cluster 3 (43% outbreaks detected), Cluster 1 (59% of outbreaks detected) and Cluster 2 (97% of outbreaks detected). This may also be affected by the length of the outbreak. The Cluster 3 had only one day to be detected within the outbreak interval. In many cases the outbreak occurred before the increase had a chance to be registered. Cluster 2, which is up to 11 days long, allows greater time for the increase to develop. For instance, the Z method detected 97% of Cluster 2 outbreaks. Approximately, 60% of those were detected after the second day.

These results are consistent with the findings of Murphy who found 60% detection of "Slow-building" outbreaks using the same z-score methodology. However, the present study greatly improves on the results in the Jackson study looking at C1 and C3 performance for small outbreaks. (**See Section 5.5**) In the study only 10% of outbreaks under 5 cases were detected by the two methods. This can be explained by the mean and standard deviation of the underlying baselines chosen for the study. The lowest volume was for pneumonia hospitalizations with a mean of 2 cases per day with a SD of 1.6 cases per day with the highest volume represented by a general respiratory syndrome with a mean of 60 cases per day and a SD of 16. Because Murphy presents his findings in aggregate, it is impossible to tell the C1 and C3 performance on just the pneumonia time series. This study affirms C1 and C3 would far exceed only 10% performance given a lower volume baseline.

10.3 LIMITATONS

The practice of syndromic surveillance relies on the timely identification of outbreaks. Given the nature of bioterrorism, events will unfold over hours or minutes. The availability of data for the study limited the level of granularity of the analysis. Ideally, the study would provide the number of hours or minutes that it took a detection method to identify an outbreak. The data limitation existed for several reasons. The first was for privacy concerns. At the time of the study, there existed no practical way to mask the exact time of events without violating HIPPAA privacy rules. Events were uniformly masked at the day level but all times below that level were obscured. Secondly, the nature of data processing does not always allow for timely analysis. For instance, the time between the Emergency Department physicians history and physical and the

time to transcription of that report varies greatly. It is possible to report the number of hours or minutes between medical procedures or examinations but the results would not necessarily reflect the actual time it would take to make the data available for syndromic surveillance. In most cases, the results would overestimate the timeliness of the system.

Aim 1 and Aim 2 rely on the analysis of clinical data. The gold standard for a study of this nature would be to examine each of these patients prospectively and record the presence of various indicators. The expense and logistics of physicians being employed on the study prohibited this approach. Another approach would have been to retrieve all the paper charts for the patients included in the study. Resources did not exist to undertake such an extensive chart abstraction. The approach of the study relied on the availability of the data in electronic format in the MARS system.

10.4 RECOMMENDATIONS

This study has brought to light the importance of future research in the field of syndromic surveillance as well as implications for public health practice. The ability of newly implemented electronic health records (EHR) to provide data for syndromic surveillance requires further study. Once it is understood what data is available and the quality of such data, public health practitioners can begin the process of putting surveillance protocols in place which rely on a greater interchange of electronic health record data between health care providers and public health authorities. This work should occur at both the patient and population level. At a patient level, electronic health records can prompt practicing physicians to immediately investigate a case of possible anthrax using decision supports. Population level monitoring can occur at

several levels and each requires understanding of implications for surveillance whether at a single provider, health system, region, state or national level. It is not clear that privacy protocols are in place to allow sharing of data across jurisdictions to conduct syndromic surveillance using newly available EHRs. Public health practitioners will soon need to undertake policymaking in this area.

From a research perspective, there are several key areas which require future inquiry. Clinical data is by necessity unstructured for certain medical records. The more that can be done to structure this data, the greater the accuracy of syndromic systems. For instance, the measured temperature of a patient should be made available electronically in a standardized format. This one piece of data would allow the objective measure of a patient's temperature as opposed to the interpretation required from extracting the word 'fever' (or 'febrile' or 'feverish' etc.) from a chief complaint. Across a region, it would be possible to take the temperature of a county or even state.

APPENDICES

Appendix A. Cutaneous Anthrax Cases

Author	Reference	Age	Sex	Year	Location	Outcome	Country
Symonds	292	38	M	1885	London	Death	England
Browne	293	30	F	1894	W. Bromwich	Recovered	England
Robinson	294	13	M	1897	London	Recovered	England
Robinson	294	37	M	1897	London	Recovered	England
Neave	295	50	M	1900		Death	England
Clarke	296	17	M	1900		Recovered	England
Mutschler	297	21	M	1900	PA	Recovered	US
Kidd	298	27	M	1900		Recovered	England
Mutschler	297	44	M	1901	PA	Recovered	US
Wilson	299	59	M	1907	Lavenham	Death	England
Clarke	300	28	M	1908		Recovered	England
Clarke	300	NS	M	1908		Recovered	England
Roberts	301	27	M	1908	Inverness	Recovered	Scotland
Fallon	302	40	M	1914	NV	Death	US
Bennett	303	30	M	1915	Aldershot	Recovered	England
Snell	304	34	M	1916	Coventry	Death	England
Gilmour	305	NS	M	1918		Death	Canada
Gilmour	305	NS	M	1918		Death	Canada
Pernet	306	26	M	1920	London	Not Specified	England
Anonymous	62	NS	M	1924	Copenhagen	Death	Denmark
Cowan	32	68	M	1928	ND	Death	US
Rankin	307	53	M	1930	Edinburgh	Death	Scotland
Cowan	32	NS	M	1937	ND	Recovered	US
Cowan	32	24	M	1937	ND	Recovered	US
Cowan	32	24	M	1938	ND	Recovered	US
Cowan	32	NS	NS	1938	ND	Recovered	US
Cowan	32	35	M	1938	ND	Death	US
Steele	35	NS	NS	1945	FL	Recovered	US
Steele	35	NS	NS	1945	AR	Recovered	US
Steele	35	NS	NS	1945	AR	Recovered	US
Steele	35	NS	NS	1945	AR	Recovered	US

Appendix A. (Continued)

Author	Reference	Age	Sex	Year	Location	Outcome	Country
Steele	35	NS	NS	1945	CA	Recovered	US
Steele	35	NS	NS	1945	KY	Recovered	US
Steele	35	NS	NS	1945	KY	Recovered	US
Steele	35	NS	NS	1945	FL	Recovered	US
Steele	35	NS	NS	1945	FL	Recovered	US
Steele	35	NS	NS	1945	FL	Recovered	US
Steele	35	NS	NS	1945	CA	Recovered	US
Steele	35	NS	NS	1945	CA	Recovered	US
Steele	35	NS	NS	1945	CA	Recovered	US
Steele	35	Child	NS	1945	FL	Recovered	US
Steele	35	NS	NS	1946	NJ	Recovered	US
Hunt	308	49	M	1953	Kent	Recovered	England
Plotkin	149	35	M	1957	NH	Recovered	US
Plotkin	149	50	F	1957	NH	Recovered	US
Plotkin	149	64	F	1957	NH	Recovered	US
Plotkin	149	61	M	1957	NH	Recovered	US
CDC	309	42	M	1987	NC	Recovered	US
Taylor	310	63	M	1988	TX	Recovered	US
Smego	311	38	F	1989	Jeremie	Recovered	Haiti
Smego	311	12	M	1989	Jeremie	Recovered	Haiti
Smego	311	50	F	1989	Jeremie	Recovered	Haiti
Smego	311	7	M	1989	Jeremie	Recovered	Haiti
Smego	311	9	F	1989	Jeremie	Recovered	Haiti
WHO	312	35	M	1991	South Wales	Recovered	Australia
de Lalla	313	63	M	1991	Vincenza	Recovered	Italy
de Lalla	313	48	M	1991	Vincenza	Recovered	Italy
de Lalla	313	43	M	1991	Vincenza	Recovered	Italy
Natori	314	63	M	1994	Miyagi	Recovered	Japan
Mallon	315	57	M	1997	London	Recovered	England
CDC	316	67	M	2000	ND	Recovered	US
Freedman	317	0.58	M	2001	NY	Recovered	US
CDC	318	NS	M	2002	TX	Recovered	US

Appendix B. Inhalational Anthrax Cases

Author	Ref	Case	Age	Sex	Year	Location	Country
Bell	319	2	55	M	1876	Bradford	England
Bell	319	1	58	M	1877	Bradford	England
Bell	319	5	NS	M	1878	Bradford	England
Bell	319	6	23	M	1878	Bradford	England
Bell	319	7	27	M	1878	Bradford	England
Bell	320	8	39	M	1878	Bradford	England
Bell	320	9	37	M	1878	Bradford	England
Bell	320	10	55	M	1878	Bradford	England
Bell	321	1	43	M	1880	Bradford	England
Bell	322	1	40	M	1880	Bradford	England
Bell	319	3	54	M	1880	Bradford	England
Bell	319	4	37	M	1880	Bradford	England
Bell	321	5	NS	M	1880	Bradford	England
Bell	321	6	39	M	1880	Bradford	England
Bell	323	1	72	M	1881	Bradford	England
Wilmot	324	1	41	M	1883	Bradford	England
Tunstall	325	1	42	M	1897	Denholme	England
Brachman	151	2	50	F	1948	PA	US
Brachman	151	1	28	M	1954	PA	US
Plotkin	149	1	60	M	1957	NH	US
Plotkin	149	2	49	M	1957	NH	US
Plotkin	149	3	65	F	1957	NH	US
Plotkin	149	4	46	M	1957	NH	US
Plotkin	149	8	33	M	1957	NH	US
Vessal	153	1	16	F	1975	Shiraz	Iran
Vessal	153	2	34	F	1975	Shiraz	Iran
Severn	326	1	53	M	1976	Northhamptonshire	England
Suffin	152	1	32	M	1976	CA	US
LaForce		1	46	M	1976	NH	US

Appendix C. Signal Investigations

Study	Forecast	Anamoly	Validation	Assess seasonality	Result
Besculides	Serfling	14 day CUSUM	Seasonal influenza	Graphed with seasonal illness	Age specific signals during flu season
Hanslik		Control chart			19 signalss @ 99.7% CI
Heffernan	14 day baseline	SatScan	Seasonal influenza	Graphical comparison with seasonal illness	14 of 22 citywide resp/21 of 22 citywide fever signals during peak Flu A and Flu B season
Meyer	Poisson Regression Model	Farrington Exceedence Score	Investigation		16 signals, 3 sources, none real
Meyer	1-12 months Historical Average	CUSUM	Investigation		79 signals, 4 sources, no real
Mostashari	Serfling	99% UCI	Seasonal Influenza		24 alarms (21 during flu season)
Mostashari	Serfling	95% UCI	Seasonal Influenza		45 alarms (21 during flu season)

Appendix D. Seasonal Correlations

Study	Method	Test	Forecast	Data Source	Measures of Accuracy	Result
Carrat	Regression, Serfling	90% Threshold	Seasonal Influenza	Comparison with seasonal illness		
Cooper	Regression, Poisson			GP ILI and Positive Influenza Tests	Correlation with GP ILI Reporting;	R2 = 0.51
Costaglia	Regression, Serfling	2 SD for 2 weeks	Seasonal Influenza	Comparison with seasonal illness		Figure 1
Choi	Regression, ARIMA		P&I deaths	P&I deaths	Relative error	AVG 1.4%; SD 10.9%
Reis	Regression, ARIMA		Respiratory visits	ED CC	Mean absolute percentage error	27.54%
Choi	Regression, Serfling		P&I deaths	P&I deaths	Relative error	AVG 1.9%; SD 13.0%
Flamand	Moving Average, 7day	2sigma	Seasonal Influenza	Correlation with seasonal illness	CC	0.92
Lazarus	Regression, GLMM	p-value	Seasonal Influenza	Graphical comparison with seasonal illness	Spearman	0.89
Lazarus	Regression, GLMM	p-value	Seasonal Influenza	Graphical comparison with seasonal illness		
Lewis	Regression, ARIMA	95% UCI	Seasonal Influenza	Correlation with seasonal illness	Spearman	0.704
Miller	Regression, PROC AUTOREG	CUSUM	Simulation	Correlation with seasonal illness;	Pearson same week 0.41 previous week 0.41 ;	0.41
Mostashari	Regression, Serfling			Seasonal Influenza	Correlation with seasonal illness	R squared 76%; 121 alarms
Tsui	Regression, Serfling	95% UCI	Seasonal Influenza	Discuss seasonal illness		
Vergu	Regression		ILI incidence	OTC sales	Correlation coefficient	0.94
Viboud	Regression		ILI incidence	GP reports	Correlation coefficient	0.9

Appendix E. Case Series of Cutaneous Anthrax

Cutaneous Anthrax Cases
1987, North Carolina - Small, red, pruritic, papular lesion on right forearm. Over the next week, the lesion became vesiculated and then developed a depressed black eschar with surrounding edema. Patient was hospitalized with worsening edema, pain, fever, and chills. Recovered. (309)
1988, Texas - First noticed a purplish, pruritic papule on the exterior surface of the left forearm distally. Illness characterized by left arm pain and edema. Necrotic lesion on left forearm with cellulitis and lymphadenopathy by the time patient came for outpatient care complaining of "spider bite". Physical exam revealed no acute distress. A 3 cm necrotic eschar was present on the exterior surface of the distal aspect of the left forearm, surrounded by a border of non-pitting gelatinous edema. Recovered. (310)
2000, North Dakota - Four days after disposing of five cows that had died of anthrax patient noticed a small bump on his left cheek at the angle of his jaw. On August 25, the lesion had enlarged and he sought medical attention. Patient denied fever, malaise, headache, pruritus, or difficulty swallowing. On examination, the lesion was indurated to approximately the size of a quarter and was surrounded by a purple colored ring. The patient was afebrile and did not appear ill. The physician reported a firm, nontender, superficial nodule with an overlying 0.5 cm black eschar. Recovered. (316)
2001, New York - Infant admitted to hospital. On admission, the infant was alert, afebrile, and in no apparent distress. Two days prior to admission he was noted to have a painless red macule on the proximal medial aspect of the left upper extremity with associated swelling. During the next 24 hours, the arm became increasingly edematous, the macule evolved to a papule, and a slight serous drainage began. On hospital day 2, the left arm showed massive, nonpitting, nontender edema with a dark red macule approximately 2 to 3 cm in diameter. There was copious, yellow serous drainage from the wound and paler erythema extending across the anterior thorax to the sternum. Later that day, the patient became febrile (39.2°C) and developed significant thrombocytopenia. Recovered. (317)
2002, Texas - A laboratory worker noticed a small bump on his right jaw while shaving, which bled briefly and then became itchy and irritated. During the next 2--3 days, the worker's facial wound increased in size and developed a scab. He also reported right cervical adenopathy, a low-grade fever, and swelling and erythema on his right cheek and neck. Recovered. (318)

Appendix F. Case Series of Gastrointestinal Anthrax

Gastrointestinal Anthrax Cases
1970, Iran - Patient developed chills and fever one week before admission. Fever subsided two days after admission. Abdomen size and discomfort increased. Admitted with restlessness, dehydration, confusion, and in acute distress. Abdomen markedly distended by ascites. Progressed to hypotension and shock. Fatal. (327)
1995, Iran - 2 year old girl admitted with history of fever, nausea, vomiting, and loose stools followed by restlessness, blood tinged vomit, and abdominal distention. Soon after developed shock. Dehydration, restless, confusion, and acute distress followed. She had mild cyanosis with cold extremities. Her condition steadily deteriorated. Fatal. (328)
1997, Turkey - 40 year old woman developed chills and fevers three days before hospital admission. She was restless, confused, dehydrated, and afebrile. Her abdomen was distended and tense. She complained of constant generalized abdominal pain with rebound tenderness. which was more severe in the lower right quadrant. Next day, patient's bowel sounds disappeared and her abdomen became more distended and tender. Rectal exam revealed small amount of blood. Recovered. (329)

Appendix G. Case Series of Anthrax with Meningitis Complications

Meningitis
1989, Iran - 2 year old girl admitted in poor general condition. She had high fever, right focal seizures, and bilateral soft tissue swelling of 2.5 to 3.0 cm diameter on the parietal area of the skull. Neurologic exam revealed ptosis, with pupillary dilation of the right eye. The patient died within 3 hours. Fatal. (330)
1997, Turkey - 64 year old man admitted to a hospital with high fever, shortness of breath, and unconsciousness. Complained three days earlier of malaise, headache, and abdominal pain. Patient was comatose and pupils were dilated. Neurologic examination revealed indefinite meningeal signs without neck rigidity. Corneal and deep tendon reflexes were negative and the patient did not respond to painful stimuli. The right retroauricular region and neck were slightly swollen and hyperemic. The patient died after 20 hours. Fatal. (331)
1997, Hong Kong - 13 year old boy admitted with 4 day history of vomiting and diarrhea. Complained of slowly progressive headache and right lower quadrant abdominal pain. Patient remained febrile and became confused 5 hours after admission. Condition deteriorated rapidly and he became comatose and developed shock. Fatal. (332)

Appendix H. IRB Approval

University of Pittsburgh
Institutional Review Board

Exempt and Expedited Reviews
Christopher M. Ryan, Ph.D., Vice Chair

3500 Fifth Avenue
Suite 105
Pittsburgh, PA 15213
Phone: 412.578.3424
Fax: 412.578.8566
e-mail: irbexempt@msx.upmc.edu

TO: Nicholas Soulakis

FROM: Christopher M. Ryan, Ph.D., Vice Chair

DATE: 7/22/2003

PROTOCOL: Characterization of Patients with Features Consistent with Inhalation Anthrax in an Emergency Department Population

IRB Number: 0307028

The above-referenced protocol has been reviewed by the University of Pittsburgh Institutional Review Board. This protocol meets all the necessary requirements and is hereby designated as "exempt" under section 45 CFR 46.101(b)(4). Exempt protocols must be re-reviewed every three years. If you wish to continue the research after that time, a new application must be submitted.

- If any modifications are made to this project, please submit an 'exempt modification' form to the IRB.
- Please advise the IRB when your project has been completed so that it may be officially terminated in the IRB database.
- This research study may be audited by the University of Pittsburgh Research Conduct and Compliance Office.

Approval Date: 7/22/2003
Renewal Date: 7/22/ 2006

CR/ky

Appendix I. Form 1 Instructions

TITLE: FORM 1 INSTRUCTIONS - RADIOLOGY REPORT REVIEW	FILENAME: FORM_01_INSTRUCTIONS_030924.vsd

STUDY: Characterization of Patients with Features Consistent with Inhalation Anthrax in an Emergency Department Population

FORM 1 INSTRUCTIONS - RADIOLOGY REPORT REVIEW

PURPOSE

These instructions describe the use of Form 1 to identify patients with findings consistent with inhalation anthrax from full-text radiology reports. The two radiologic findings of interest for Form 1 are mediastinal widening or hilar, paratracheal, peribronchial, or mediastinal lymphadenopathy.

REVIEW PROCEDURE

Each radiology report is printed separately. Reports with more than one page are stapled. Complete the form at the bottom of the last page. If an error occurs in marking the form, please cross out and initial the error. Review of each report requires the completion of two questions.

Question A ascertains the presence of a widened mediastinum. If a report positively identifies the patient as having a widened mediastinum, choose YES. If the report indicates the patient does not have a widened mediastinum or indicates the mediastinum is normal, choose NO. A report which does not mention the mediastinum should be marked NOT SPECIFIED. If a report does not contain enough evidence to choose YES, but NO or NOT SPECIFIED does not accurately identify the record, choose UNCERTAIN. One example of this circumstance is a report which refers to a prior report or to an image. All reports are to be considered independently of outside evidence. Another example is a report containing phrases or terms relating uncertainty such as 'may be', 'may represent', 'suggesting', or 'possibly'. Without additional evidence in the report, further review is required to ascertain whether the patient had mediastinal widening. Also, some reports will attribute the finding of interest to technique or positioning. These reports would need further review. The HISTORY may specify the patient had the finding of interest in the past. This requires further review because it is based on history not the current radiograph.

Question B establishes the presence of lymphadenopathy. If the report positively identifies the patient as having lymphadenopathy, choose YES. Any YES report requires further characterization. Four types of lymphadenopathy are specifically addressed: hilar, paratracheal, peribroncheal, or mediastinal. Choose the appropriate box if any of these is present. Lymphadenopathy of any other location is indicated by choosing the OTHER LOCATION box. If no mention of the location is made, choose NOT SPECIFIED. If a report indicates a patient does not have lymphadenopathy or that the lymph nodes are normal, choose NO. A report which does not mention lymphadenopathy should be marked as NOT SPECIFIED. Reports with insufficient evidence should be marked as UNCERTAIN.

A NOTES section has been included for any reviewer comments on the report; whether to themselves or to the study investigators. The NOTES section is optional and not required for completion of the review of the report.

A patient may have multiple reports. If question A or B is YES at any time in any of the reports, the form should be marked as YES.

ATTESTATION

Once questions A and B have been marked, initial and date the form attesting to your completed review of the report.

CONFIDENTIALITY

Although the reports have been stripped of patient identifiers, they should be stored in a secure and private location throughout the review process; conforming to the requirements of HIPAA.

RETURN OF REPORTS

All reports, whether completed or not, will be returned to the study investigators. A predetermined time period allowed for the review of the reports will be agreed upon between reviewers and investigators. This will be communicated in the initial reviewer meeting.

Last Edit Date: 10/1/2005 , 2:23:27 PM

COMPANY: UNIVERSITY OF PITTSBURGH	CREATOR: Nicholas Soulakis

Appendix J. Form 1– Radiologic Findings

TITLE: FORM 1 - RADIOLOGY REPORT REVIEW	FILENAME: FORM_01_030811A.vsd	RECNO: 6741

S_O_H
Counters Account Number Principal Date Record Type
204,2m5e2quzyaQS NICK-6741 Mar 28 2001 RAD
E_O_H
[Record de-identified by: De-ID ver.5.10]

PORTABLE CHEST: 3-28-01 0555 HRS.

The heart is normal. Trachea is at the midline. Partial obscuration of the right hilum by the tortuous thoracic aorta.

There is minimal fluid within the right minor fissure.

There is borderline interstitial edema with no midline shift.

Left chest tube at the apex. Subcutaneous emphysema over the neck and over the left chest wall.

IMPRESSION:

1. CARDIAC SIZE IS NORMAL. MINIMAL FLUID WITHIN THE RIGHT MINOR FISSURE. BORDERLINE INTERSTITIAL EDEMA WITH NO PNEUMOTHORAX.
2. LEFT CHEST TUBE LATERAL TO THE LEFT APEX.

M28

My signature below is attestation that I have interpreted this/these examination(s) and agree with the findings as noted above.

END OF IMPRESSION:

E_O_R

rev:6/12/2006 1:39:04 PM

A. Widened Mediastinum? ☐ Yes ☐ No ☐ Not specified ☐ Uncertain

B. Lymphadenopathy? ☐ Yes ☐ No ☐ Not specified ☐ Uncertain

Location: ☐ Hilar ☐ Mediastinal ☐ Paratracheal ☐ Peribronchial ☐ Other Location ☐ Not Specified

Note: _____

Reviewer Initials: _____ **Date:** _____

Appendix K. Form 1 Tie-break Form

TITLE: FORM 1 - RADIOLOGY REPORT REVIEW FORM	FILENAME: FORM_01_TIE_060612.vsd	RECNO: 6741

S_O_H
Counters Account Number Principal Date Record Type
204,2m5e2quzyaQS NICK-6741 Mar 28 2001 RAD
E_O_H
[Record de-identified by: De-ID ver.5.10]

PORTABLE CHEST: 3-28-01 0555 HRS.

The heart is normal. Trachea is at the midline. Partial obscuration of the right hilum by the tortuous thoracic aorta.

There is minimal fluid within the right minor fissure.

There is borderline interstitial edema with no midline shift.

Left chest tube at the apex. Subcutaneous emphysema over the neck and over the left chest wall.

IMPRESSION:

1. CARDIAC SIZE IS NORMAL. MINIMAL FLUID WITHIN THE RIGHT MINOR FISSURE. BORDERLINE INTERSTITIAL EDEMA WITH NO PNEUMOTHORAX.
2. LEFT CHEST TUBE LATERAL TO THE LEFT APEX.

M28

My signature below is attestation that I have interpreted this/these examination(s) and agree with the findings as noted above.

END OF IMPRESSION:

E_O_R

rev:6/12/2006 1:48:32 PM

A. Widened Mediastinum? ☐ Yes ☐ No ☐ Not specified ☐ Uncertain

B. Lymphadenopathy? ☐ Yes ☐ No ☐ Not specified ☐ Uncertain

Location: ☐ Hilar ☐ Mediastinal ☐ Paratracheal ☐ Peribronchial ☐ Other Location ☐ Not Specified

Note: _____

Reviewer 1 Initials: _____ **Date:** _____

Reviewer 2 Initials: _____ **Date:** _____

Appendix L. Form 2 Instructions

TITLE: FORM 2 Instructions - Medical History & Physical Exam Review FILENAME: FORM_02_INSTRUCTIONS_030923A.vsd

STUDY: "Characterization of Patients with Features Consistent with Inhalation Anthrax in an Emergency Department Population"

PURPOSE
These instructions describe the use of Form 2 to review full-text patient Emergency Department [ED] reports.

REVIEW PROCEDURE
Each ED report is printed separately. Reports with more than one page will be stapled. Complete the form on the last page. If an error occurs in marking the form, please cross out and initial the error. Review of each report requires the completion of CHIEF COMPLAINT and two checklists - MEDICAL HISTORY and SIGNS AND SYMPTOMS. Every item must be marked. If CHIEF COMPLAINT cannot be completed, mark 'NA'. Where applicable, please print legibly. Include a clear description of any shorthand used for the review on the ABBREVIATIONS sheet.

MEDICAL HISTORY
If a report positively identifies the patient as having any of the comorbid conditions in the medical history listing, choose YES [Y] for that item. SUPPLEMENT TO FORM 2 defines 'comorbid condition' and provides a more detailed listing of the comorbities contained in each category.

If the report indicates the patient does not have an item in the medical history listing or does not have a significant medical history [i.e. previously healthy], choose NO [N] for that item. If a report does not contain enough evidence to choose YES for an item, but NO does not accurately identify the report, choose UNCERTAIN [U]. One example of this circumstance is a report which refers to a prior report or to an image. All reports are to be considered independently of outside evidence. Another example is a report containing phrases or terms relating uncertainty such as 'may be', 'may represent', 'suggesting', or 'possibly'. Without additional evidence in the report, further review is required to ascertain whether the patient has had the item.

The lack of mention of a specific comorbid condition in these reports cannot be interpreted as the absence of that finding from the patient's medical history. Each item that is not mentioned in the report should be marked as NOT SPECIFIED [NS]. Any disease not included in the 17 categories but is likely to be a significant factor influencing mortality or resource use in the hospital should be added to a patient's list of 'OTHER' comorbid conditions.

SIGNS AND SYMPTOMS
If a report positively identifies the patient as having any of the signs or symptoms in the physical examination listing, choose YES [Y] for that item.

If the report indicates the patient does not have an item in the physical exam listing, choose NO [N] for that item. If a report does not contain enough evidence to choose YES for an item, but NO does not accurately identify the report, choose UNCERTAIN [U]. Reports with uncertainty or insufficient evidence should be marked as UNCERTAIN. Each item that is not mentioned in the report should be marked as NOT SPECIFIED [NS].

NOTES
This section has been included for any reviewer comments on the report; whether to themselves or to the study investigators. The NOTES section is optional and not required for completion of the review of the report.

ATTESTATION
Once MEDICAL HISTORY and SIGNS AND SYMPTOMS have been marked, initial and date the form attesting to your completed review of the report.

CONFIDENTIALITY
Although the reports have been stripped of patient identifiers, they should be stored in a secure and private location throughout the review process; conforming to the requirements of HIPAA.

RETURN OF REPORTS
All reports, whether completed or not, will be returned to the study investigators. A predetermined time period allowed for the review of the reports will be agreed upon between reviewers and investigators. This will be communicated in the initial reviewer meeting.

DATE: 11/21/2003 TIME: 3:27:21 PM PG: 1 OF 1 PGS

Appendix M. Form 2 Supplement for Medical History Definitions

DATE: 11/21/2003	TIME: 3:18:31 PM	PG: 1 OF 3 PGS
TITLE: SUPPLEMENT TO FORM 2		FILENAME: SUPPLEMENT02_030923.vsd

Comorbidity: A clinical condition that exists before a patient's admission to the hospital and is likely to be a significant factor influencing mortality and resource use in the hospital [Elixhauser 1998].

The comorbid conditions below are explicitly defined in:

Charlson et al. "A New Method for Classifying Prognostic Comorbidity in Longitudinal Studies: Development & Evaluation." J Chron Dis Vol 40. No. 5, pp 373-383. 1987.

Deyo et al. "Adapting a Clinical Comorbidity Index for Use with ICD-9-CM Administrative Databases." J Clin Epidemiol Vol 45. No. 9, pp 613-619. 1992.

Romano et al. "Adapting a Clinical Comorbidity Index for Use with ICD-9-CM Administrative Data: Differing Perspectives." J Clin Epidemiol Vol 46. No. 10, pp 1075-1079. 1993.

Myocardial Infarction
Acute myocardial infarction
Old myocardial infarction

Congestive heart failure
Hypertensive heart disease
Cardiomyopathy
Heart failure
Ill-defined descriptions & complications of heart disease

Peripheral vascular disease
Atherosclerosis
Aortic aneurysm & dissection
Other aneurysm
Other peripheral vascular disease
Other disorders of arteries & arterioles
Symptoms involving cardiovascular system

Cereberovascular disease
Other retinal disorders
Subarachnoid hemorrhage
Intracerebral hemorrhage
Other & unspecified intracranial hemorrhage
Occlusion & stenosis of precerebral arteries
Occlusion of cerebral arteries
Transient cerebral ischemia
Acute, but ill-defined, cerebrovascular disease
Other cerebrovascular disease
Late effects of cerebrovascular disease
Symptoms involving nervous & musculoskeletal systems
Symptoms involving head & neck
Complications affecting specified body systems, not elsewhere classified

Dementia
Senile & presenile organic psychotic conditions
Other cerebral degenerations

Chronic pulmonary disease **[continued on next page]**
Acute pulmonary heart disease
Chronic pulmonary heart disease
Bronchitis, not specified as acute or chronic
Chronic bronchitis
Emphysema
Asthma

Appendix N. Form 2 Supplement for Medical History Definitions

Chronic pulmonary disease cont...
Bronchiectasis
Extrinsic allergic alveolitis
Chronic airway obstruction, not elsewhere classified
Coal workers' pneumoconiosis
Asbestosis
Pneumoconiosis due to other silica or silicates
Pneumoconiosis due to other inorganic dust
Pneumonopathy due to inhalation of other dust
Pneumoconiosis, unspecified
Respiratory conditions due to chemical fumes & vapors

Rheumatologic disease
Diffuse diseases of connective tissue
Rheumatoid arthritis & other inflammatory polyarthropathies
Polymyalgia rheumatica

Peptic Ulcer disease
Gastric ulcer
Duodenal ulcer
Peptic ulcer, site unspecified
Gastrojejunal ulcer

Mild liver disease
Chronic liver disease & cirrhosis

Diabetes mellitus

Hemiplagia or paraplegia
Hemiplegia & hemiparesis
Other paralytic syndromes

Renal Disease
Chronic glomerulonephritis
Nephritis & nephropathy, not specified as acute or chronic
Chronic renal failure
Renal failure, unspecified
Disorders resulting from impaired renal function

Any malignancy [See Page 3]

Moderate or severe liver disease
Liver abscess & sequelae of chronic liver disease
Other disorders of liver
Cholelithiasis
Other disorders of gallbladder
Other disorders of biliary tract
Diseases of pancreas
Gastrointestinal hemorrhage
Intestinal malabsorption
Acute glomerulonephritis
Nephrotic syndrome

Metastatic solid tumor
Secondary & unspecified malignant neoplasm of lymph nodes
Secondary malignant neoplasm of respiratory & digestive systems
Secondary malignant neoplasm of other specified sites
Malignant neoplasm without specification of site

AIDS
Human immunodeficiency virus [HIV] disease

Appendix O. Form 2 Supplement for Medical History Definitions

DATE: 11/21/2003 TIME: 3:18:31 PM PG: 1 OF 3 PGS

Any malignancy
Malignant neoplasm of lip
Malignant neoplasm of tongue
Malignant neoplasm of major salivary gl&s
Malignant neoplasm of gum
Malignant neoplasm of floor of mouth
Malignant neoplasm of other & unspecified parts of mouth
Malignant neoplasm of oropharynx
Malignant neoplasm of nasopharynx
Malignant neoplasm of hypopharynx
Malignant neoplasm of other sites within the lip, oral cavity, & pharynx
Malignant neoplasm of esophagus
Malignant neoplasm of stomach
Malignant neoplasm of small intestine, including duodenum
Malignant neoplasm of colon
Malignant neoplasm of rectum, rectosigmoid junction, & anus
Malignant neoplasm of liver & intrahepatic bile ducts
Malignant neoplasm of gallbladder & extrahepatic bile ducts
Malignant neoplasm of pancreas
Malignant neoplasm of retroperitoneum & peritoneum
Malignant neoplasm of other sites within the digestive organs & peritoneum
Malignant neoplasm of nasal cavities, middle ear, & accessory sinuses
Malignant neoplasm of larynx
Malignant neoplasm of trachea, bronchus, & lung
Malignant neoplasm of pleura
Malignant neoplasm of thymus, heart, & mediastinum
Malignant neoplasm of other sites within the respiratory system & intrathoracic organs
Malignant neoplasm of bone & articular cartilage
Malignant neoplasm of connective & other soft tissue
Malignant melanoma of skin
Malignant neoplasm of female breast
Malignant neoplasm of male breast
Kaposi's sarcoma
Malignant neoplasm of uterus, part unspecified
Malignant neoplasm of cervix uteri
Malignant neoplasm of placenta
Malignant neoplasm of body of uterus
Malignant neoplasm of ovary & other uterine adnexa
Malignant neoplasm of other & unspecified female genital organs
Malignant neoplasm of prostate
Malignant neoplasm of testis
Malignant neoplasm of penis & other male genital organs
Malignant neoplasm of bladder
Malignant neoplasm of kidney & other & unspecified urinary organs
Malignant neoplasm of eye
Malignant neoplasm of brain
Malignant neoplasm of other & unspecified parts of nervous system
Malignant neoplasm of thyroid gl&
Malignant neoplasm of other endocrine gl&s & related structures
Malignant neoplasm of other sites
Lymphosarcoma & reticulosarcoma
Hodgkin's disease
Other malignant neoplasms of lymphoid & histiocytic tissue
Multiple myeloma & immunoproliferative neoplasms
Lymphoid leukemia
Myeloid leukemia
Monocytic leukemia
Other specified leukemia
Leukemia of unspecified cell type

Appendix P. Form 2 – Medical History and Physical Findings

TITLE: FORM 2 - Emergency Department Report Review Last Edit: 6/12/2006 2:08:34 PM

RECORD NUMBER: 4404

S_O_H
Counters Account Number Principal Date Record Type
2,xT4U3Fc/yK+T NICK-4404 May 24 2001 ER
E_O_H
[Record de-identified by: De-ID ver.5.08]

HISTORY OF PRESENT ILLNESS:

The patient is an 80-year-old white male who presents to the emergency department with complaints of not feeling well and being too sick to stay at home. The patient was seen in the emergency department yesterday at which time he had complaints of nausea, weakness, and fatigue. The patient was thought to have had too much of a dose of OxyContin which he had started recently for back pain. The symptoms that he exhibited yesterday were attributed to this and he was discharged ambulatory to home with instructions to take half of the dose prescribed rather than two times the dose prescribed, and to follow up with his primary care physician. He presents today because he is not feeling well. His main complaints are sore throat, difficulty swallowing, and constipation. The patient states that he has not felt well, has been increasingly weak, and feels that he is unsafe to stay at home.

REVIEW OF SYSTEMS:

GENERAL: Generally, the patient's health has been decreased over the past 24 hours. He feels weak and feels that he needs to hold onto the furniture to get around the house. He does not ambulate with an assistive device. The patient states that he has not taken his temperature, but feels warm.

HEENT: Eyes: The patient wears corrective lenses. He denies any blurred vision or double vision. Ears: No change in hearing, no discharge, and no pain. Nose: The patient has had nasal congestion. He denies any epistaxis. Mouth: The patient has had a sore throat. He states it is painful to swallow, and therefore, he has limited his oral intake of food and fluids.

NECK: No neck pain or immobility.

RESPIRATORY: The patient has a history of left lung cancer. He denies any productive cough. The patient has had a dry cough and a feeling of shortness of breath.

CARDIAC: The patient denies any chest pain, orthopnea, or ankle edema. He is status post insertion of a pacemaker. The patient also has a history of coronary artery disease and has had placement of four stents. He denies any current chest pain.

GI: The patient complains of slight nausea. He has had no vomiting. He denies any diarrhea. The patient's last bowel movement was yesterday. The patient feels that his constipation has been aggravated by the opiate used for his back pain. He denies any hematochezia or melena.

GU: The patient is status post radical prostatectomy. He denies any dysuria or hematuria. He has nocturia two to three times per night. The patient has occasional incontinence. He is status post radiation therapy and chemotherapy also for his prostate cancer.

ENDOCRINE: The patient denies any diabetes or thyroid disease.

HEME/LYMPH: No abnormal bleeding or bruising.

NEUROLOGIC: No headache, lightheadedness, or seizure. The patient has Parkinson's disease.

PSYCHIATRIC: The patient denies any history of depression.

All others negative.

PAST MEDICAL HISTORY:

1. Osteoporosis.
2. Coronary artery disease with stenting.
3. Pacemaker.
4. Left lung cancer.
5. Gait disturbance.
6. CVA.

CHIEF COMPLAINT

_____

_____

PAST MEDICAL HISTORY

Y N U NS Myocardial infarction
Y N U NS Congestive heart failure
Y N U NS Peripheral vasc. disease
Y N U NS Cerebrovascular disease
Y N U NS Dementia
Y N U NS Chronic pulm. disease
Y N U NS Rheumatologic disease
Y N U NS Peptic ulcer disease
Y N U NS Mild liver disease
Y N U NS Diabetes mellitus
Y N U NS Hemiplegia or paraplegia
Y N U NS Renal disease
Y N U NS Any malignancy
Y N U NS Mod. or sev. liver disease
Y N U NS Metastatic solid tumor
Y N U NS AIDS

Other 1_____
Other 2_____
Other 3_____
Other 4_____

SIGNS AND SYMPTOMS

Y N U NS Fever
Y N U NS Sweats
Y N U NS Fatigue
Y N U NS Cough
Y N U NS Dementia
Y N U NS Dyspnea
Y N U NS Nausea or Vomiting
Y N U NS Chest Discomfort or Pain
Y N U NS Myalgias
Y N U NS Headache
Y N U NS Confusion
Y N U NS Abdominal Pain
Y N U NS Sore Throat
Y N U NS Rhinorrhea

Initials: _____ Date: _____

Note: _____

_____

_____

Appendix Q. Form 2 Tie-break

TITLE: FORM 2 - Emergency Department Report Tie Break Form Last Edit: 2/18/2004 9:25:18 PM

RECORD NUMBER: 4404

S_O_H
Counters Account Number Principal Date Record Type
2,xT4U3Fc/yK+T NICK-4404 May 24 2001 ER
E_O_H
[Record de-identified by: De-ID ver.5.08]

HISTORY OF PRESENT ILLNESS:

The patient is an 80-year-old white male who presents to the emergency department with complaints of not feeling well and being too sick to stay at home. The patient was seen in the emergency department yesterday at which time he had complaints of nausea, weakness, and fatigue. The patient was thought to have had too much of a dose of OxyContin which he had started recently for back pain. The symptoms that he exhibited yesterday were attributed to this and he was discharged ambulatory to home with instructions to take half of the dose prescribed rather than two times the dose prescribed, and to follow up with his primary care physician. He presents today because he is not feeling well. His main complaints are sore throat, difficulty swallowing, and constipation. The patient states that he has not felt well, has been increasingly weak, and feels that he is unsafe to stay at home.

REVIEW OF SYSTEMS:

GENERAL: Generally, the patient's health has been decreased over the past 24 hours. He feels weak and feels that he needs to hold onto the furniture to get around the house. He does not ambulate with an assistive device. The patient states that he has not taken his temperature, but feels warm.

HEENT: Eyes: The patient wears corrective lenses. He denies any blurred vision or double vision. Ears: No change in hearing, no discharge, and no pain. Nose: The patient has had nasal congestion. He denies any epistaxis. Mouth: The patient has had a sore throat. He states it is painful to swallow, and therefore, he has limited his oral intake of food and fluids.

NECK: No neck pain or immobility.

RESPIRATORY: The patient has a history of left lung cancer. He denies any productive cough. The patient has had a dry cough and a feeling of shortness of breath.

CARDIAC: The patient denies any chest pain, orthopnea, or ankle edema. He is status post insertion of a pacemaker. The patient also has a history of coronary artery disease and has had placement of four stents. He denies any current chest pain.

GI: The patient complains of slight nausea. He has had no vomiting. He denies any diarrhea. The patient's last bowel movement was yesterday. The patient feels that his constipation has been aggravated by the opiate used for his back pain. He denies any hematochezia or melena.

GU: The patient is status post radical prostatectomy. He denies any dysuria or hematuria. He has nocturia two to three times per night. The patient has occasional incontinence. He is status post radiation therapy and chemotherapy also for his prostate cancer.

ENDOCRINE: The patient denies any diabetes or thyroid disease.

HEME/LYMPH: No abnormal bleeding or bruising.

NEUROLOGIC: No headache, lightheadedness, or seizure. The patient has Parkinson's disease.

PSYCHIATRIC: The patient denies any history of depression.

All others negative.

PAST MEDICAL HISTORY:

1. Osteoporosis.
2. Coronary artery disease with stenting.
3. Pacemaker.
4. Left lung cancer.
5. Gait disturbance.
6. CVA.

CHIEF COMPLAINT

_____

_____

PAST MEDICAL HISTORY

Y N U NS Myocardial infarction
Y N U NS Congestive heart failure
Y N U NS Peripheral vasc. disease
Y N U NS Cerebrovascular disease
Y N U NS Dementia
Y N U NS Chronic pulm. disease
Y N U NS Rheumatologic disease
Y N U NS Peptic ulcer disease
Y N U NS Mild liver disease
Y N U NS Diabetes mellitus
Y N U NS Hemiplegia or paraplegia
Y N U NS Renal disease
Y N U NS Any malignancy
Y N U NS Mod. or sev. liver disease
Y N U NS Metastatic solid tumor
Y N U NS AIDS

Other 1_____
Other 2_____
Other 3_____
Other 4_____

SIGNS AND SYMPTOMS

Y N U NS Fever
Y N U NS Sweats
Y N U NS Fatigue
Y N U NS Cough
Y N U NS Dementia
Y N U NS Dyspnea
Y N U NS Nausea or Vomiting
Y N U NS Chest Discomfort or Pain
Y N U NS Myalgias
Y N U NS Headache
Y N U NS Confusion
Y N U NS Abdominal Pain
Y N U NS Sore Throat
Y N U NS Rhinorrhea

Initials 1: _____ Date: _____

Initials 2: _____ Date: _____

_____

_____

Appendix R. Form 3 Instructions

DATE: 9/5/2003	TIME: 9:10:25 AM	PG: 1	OF 1	PGS
TITLE: FORM 3 INSTRUCTIONS - RADIOLOGY REPORT REVIEW		FILENAME: FORM_03_INSTRUCTIONS_031022.vsd		

STUDY: Characterization of Patients with Features Consistent with Inhalation Anthrax in an Emergency Department Population

PURPOSE

These instructions describe the use of Form 3 to identify patients with findings consistent with inhalation anthrax from full-text radiology reports. The two radiologic findings of interest for Form 3 are consolidation or pleural effusions. These radiologic findings are common among those suffering inhalation anthrax.

REVIEW PROCEDURE

Each radiology report is printed separately. Complete the form at the bottom of the last page. If an error occurs in marking the form, please cross out and initial the error. Review of each report requires the completion of two questions.

Question A ascertains the presence of consolidation. Terms such as 'air space disease,' 'opacity,' 'pneumonia,' or 'infiltrates' could also describe consolidation. If a report positively identifies the patient as having consolidation, choose YES. Specify the location of the consolidation for all YES reports. LOCATION is indicated by completing the RIGHT and LEFT lung fields. If only one lung is mentioned, choose NOT SPECIFIED for the other. Do not leave it blank. If no mention of the location is made in the report, choose location NOT SPECIFIED for both. Further specify the region of the lung by choosing UPPER, MIDDLE, or LOWER. If no region is indicated choose NOT SPECIFIED. If the report indicates the patient does not have consolidation or indicates the lungs are normal, choose NO. A report which does not mention consolidation should be marked NOT SPECIFIED. If a report does not contain enough evidence to choose YES, but NO or NOT SPECIFIED does not accurately identify the record, choose UNCERTAIN. One example of this is a report containing phrases or terms relating uncertainty such as 'may be', 'may represent', 'suggesting', or 'possibly'. Without additional evidence in the report, further review may be required to ascertain whether the patient had consolidation. Also, some reports will attribute the finding of interest to technique or positioning. These reports would need further review. The HISTORY may specify the patient had the finding of interest in the past. This requires further review because it is based on history not the current radiograph.

Question B establishes the presence of pleural effusions. If the report positively identifies the patient as having pleural effusions, choose YES. Any YES report requires further characterization. Specify the location and size of the pleural effusions for all YES reports. LOCATION is indicated by completing the RIGHT and LEFT lung fields. If only one lung is mentioned, choose NOT SPECIFIED for the other. Do not leave it blank. If no mention of the location is made in the report, choose location NOT SPECIFIED for both. Specify the size of the effusion by choosing LARGE, MEDIUM, or SMALL. If no size is indicated choose NOT SPECIFIED. If a report indicates a patient does not have pleural effusions or that the lungs are normal, choose NO. A report which does not mention pleural effusions should be marked as NOT SPECIFIED. Reports with uncertainty or insufficient evidence should be marked as UNCERTAIN.

A NOTES section has been included for any reviewer comments on the report; whether to themselves or to the study investigators. The NOTES section is optional and not required for completion of the review of the report.

A patient may have multiple reports. If question A or B is YES at any time in any of the reports, the form should be marked as YES.

ATTESTATION

Once questions A and B have been marked, initial and date the form attesting to your completed review of the report.

CONFIDENTIALITY

Although the reports have been stripped of patient identifiers, they should be stored in a secure and private location throughout the review process; conforming to the requirements of HIPAA.

RETURN OF REPORTS

All reports, whether completed or not, will be returned to the study investigators. A predetermined time period allowed for the review of the reports will be agreed upon between reviewers and investigators. This will be communicated in the initial reviewer meeting.

COMPANY: UNIVERSITY OF PITTSBURGH	CREATOR: Nicholas D. Soulakis

Appendix S. Form 3 – Consolidation and Pleural Effusions

TITLE: FORM 3 - RADIOLOGY REPORT REVIEW | FILENAME: FORM_03_031022.vsd | RECNO: 8932

S_O_H
Counters Account Number Principal Date Record Type
45,9kTBnphgu0Td NICK-8932 Feb 13 2001 RAD
E_O_H
[Record de-identified by: De-ID ver.5.10]

CHEST, PORTABLE AP SEMI-ERECT 2-13-01 1602 HRS

HISTORY: EVALUATE FOR INFILTRATE.

Previous chest 2-1-01. There is a large left pleural effusion which is increased from the previous study of 2-1-01. There is patchy consolidation at the right base compatible with pneumonia. The distribution would raise the possibility of aspiration. Again noted is a curvilinear foreign body projected over the lateral aspect of the left apex. The left IJ central line tip is in the SVC.

IMPRESSION:

1. LARGE LEFT PLEURAL EFFUSION. THIS IS INCREASED FROM PREVIOUS STUDY OF 2-1-01.
2. PATCHY CONSOLIDATION AT RIGHT BASE SUGGESTING PNEUMONIA. THE DISTRIBUTION WOULD RAISE THE POSSIBILITY OF ASPIRATION.

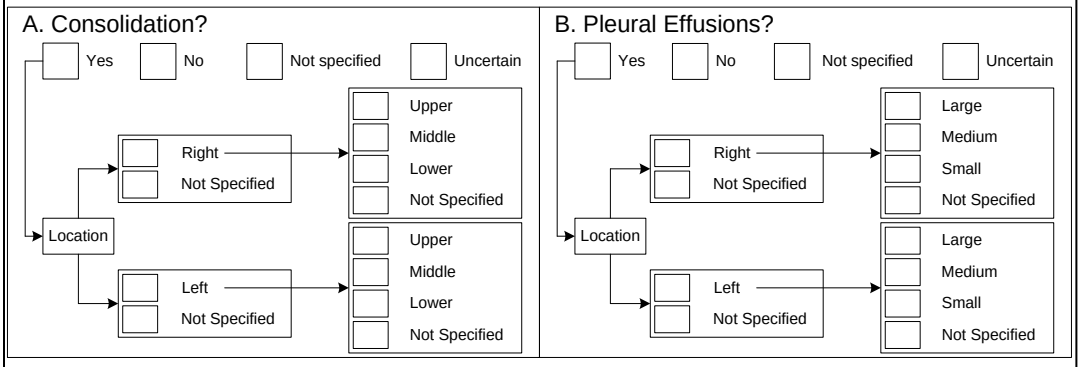
F13

My signature below is attestation that I have interpreted this/these examination(s) and agree with the findings as noted above.

END OF IMPRESSION:

E_O_R

rev:6/13/2006 1:05:00 AM



Note:

Reviewer Initials: **Date:**

Appendix T. Form 3 Tie-break

TITLE: FORM 3 - RADIOLOGY REPORT REVIEW TIE BREAK | FILENAME: FORM_03_031022_TIE_BREAKA.vsd | RECNO: 8932

S_O_H
Counters Account Number Principal Date Record Type
45,9kTBnphgu0Td NICK-8932 Feb 13 2001 RAD
E_O_H
[Record de-identified by: De-ID ver.5.10]

CHEST, PORTABLE AP SEMI-ERECT 2-13-01 1602 HRS

HISTORY: EVALUATE FOR INFILTRATE.

Previous chest 2-1-01. There is a large left pleural effusion which is increased from the previous study of 2-1-01. There is patchy consolidation at the right base compatible with pneumonia. The distribution would raise the possibility of aspiration. Again noted is a curvilinear foreign body projected over the lateral aspect of the left apex. The left IJ central line tip is in the SVC.

IMPRESSION:

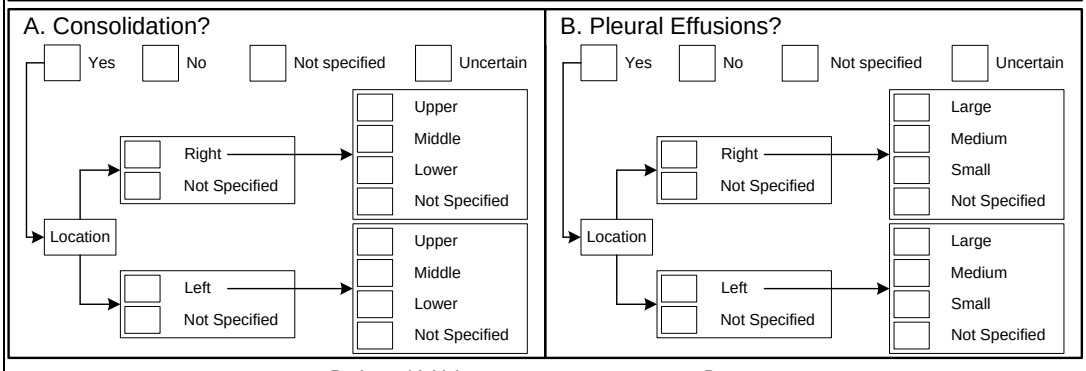
1. LARGE LEFT PLEURAL EFFUSION. THIS IS INCREASED FROM PREVIOUS STUDY OF 2-1-01.
2. PATCHY CONSOLIDATION AT RIGHT BASE SUGGESTING PNEUMONIA. THE DISTRIBUTION WOULD RAISE THE POSSIBILITY OF ASPIRATION.

F13

My signature below is attestation that I have interpreted this/these examination(s) and agree with the findings as noted above.

END OF IMPRESSION:

E_O_R



Reviewer 1 Initials: _____ Date: _____

Reviewer 2 Initials: _____ Date: _____

Appendix U. Decision Tree Analysis Results

Tree Number	Terminal Nodes	Cross-Validated Relative Cost	Complexity
1**	8	0.17	0.00
2	5	0.25	0.01
3	3	0.28	0.03
4	2	0.82	0.05
5	1	1.00	0.34

** *Optimal*

Five trees were produced of varying number of terminal nodes, cost, and complexity. CART selects the optimal tree by minimizing cost and complexity. In this case, tree number 1 with 8 terminal nodes was chosen.

Appendix V. Clinical Laboratory Results for Anthrax Patients From Medical Literature

IPSNO	PUB.	DATE	AWBC /mm3	HCT %	HGB g/dL	PLT /mm3	UREAN mg/dL	NA mmol/L	K mmol/L	CREAT mg/dL	TBILI mg/dL	AST U/L	ALT U/L	ALB g/dL	CA mg/dL
anthrax0001	BUSH	10/2/2001	9400	46	16.1	109000	20	132	3.9	1.1	1.5	30		4	8.7
anthrax0001	JERN	10/2/2001	9400	45.7		109000		132	WNL	WNL	1.5			WNL	
anthrax0002	JERN	10/1/2001	9900	47.1		WNL		WNL	WNL	1.2	WNL			2.3	
anthrax0003	JERN	10/19/2001	7500	46.9		WNL		WNL	WNL	WNL	1.9			2.9	
anthrax0003	MAYER	10/19/2001	7500												
anthrax0004	JERN	10/20/2001	9700	40.9		82000		WNL	WNL	WNL	1.7			2.9	
anthrax0004	MAYER	10/20/2001	9700												
anthrax0005	JERN	10/18/2001	10300	43		WNL		ND	ND	ND	ND			ND	
anthrax0005	BORIO	10/21/2001	18800	55.3		141000	22	130	5.3	1.6	0.9	76	77	3.1	8.5
anthrax0005	JERN	10/21/2001	18800	55		141000		130	5.3	1.6		76	77		
anthrax0006	BORIO	10/21/2001	13300	51.4		207000	20	139	4.7	1.2	0.4	39	44	3.6	7.9
anthrax0006	JERN	10/21/2001	13300	51.4		WNL		WNL	WNL	WNL	WNL			WNL	
anthrax0006	JERN	10/22/2001	31200					148		2.8					
anthrax0006	QUIN	10/22/2001	31.2	62.4	20.8	250	52	148	4.8	2.8	0.2	47	33	2.9	8.5
anthrax0007	JERN	10/24/2001	9700	45		WNL		134	3.4	WNL	ND			ND	
anthrax0007	JERN	10/25/2001	9500	48.1		215000					1.6			3	
anthrax0008	JERN	10/19/2001	8100	45.3		WNL		133	WNL	WNL	WNL			WNL	
anthrax0009	JERN	10/18/2001	11200	42.5		WNL		133	WNL	WNL	WNL			3.4	
anthrax0010	JERN	10/28/2001	11400	46.3		WNL		134	WNL	WNL	WNL			3.3	
anthrax0010	MINA	10/28/2001	11400	46.3	15.5	135000	18	134	3.5	0.8	0.1*	240	263	3.3	7.6
anthrax0011	BARA	11/16/2001	8100				39	134		1.3		45			

WNL *= Within normal limits;* ***ND*** *= Not done;* ******* *From 10/29/2001*

BARA *Barakat et al. Fatal Inhalational Anthrax in a 94-year-old Connecticut Woman. JAMA 2002; 287:863-8.*

BORIO *Borio et al. Death Due to Bioterrorism-Related Inhalational Anthrax - Report of 2 Patients. JAMA 2001; 286: 2554-2557.*

BUSH *Bush et al. Brief Report: Index Case of Fatal Inhalational Anthrax Due to Bioterrorism in the United States. NEMJ 2001; 345: 1607-1610.*

JERN *Jernigan et al. Bioterrorism-Related Inhalational Anthrax: The First 10 Cases Reported in the United States. Emerg Infect Dis 2001; 7:933-44.*

MINA *Mina et al. Fatal Inhalational Anthrax with Unknown Source of Exposure in a 61-Year-Old Woman in New York City. JAMA 2002; 287:858-862.*

NSC *Normal serum chemistry levels reported.*

NALR *Normal admission laboratory results reported.*

NE *Normal electrolytes reported.*

BIBLIOGRAPHY

1 United States Department of Health and Human Services. Fiscal Year 2013 Budget in Brief. Emergency Preparedness. http://www.hhs.gov/budget/budget-brief-fy2013.pdf (Accessed 08/09/2012).

2 United States Department of Health and Human Services. Public Health Message Regarding Anthrax Case [Press Release]. 2001 Oct 04.

3 Rotz LD, Khan AS, Lillibridge SR, Ostroff SM, Hughes JM. Public health assessment of potential biological terrorism agents. Emerg Infect Dis. 2002 Feb;8(2):225-30

4 Borio L, Inglesby T, Peters CJ, Schmaljohn AL, Hughes JM, Jahrling PB, Ksiazek T, Johnson KM, Meyerhoff A, O'Toole T, Ascher MS, Bartlett J, Breman JG, Eitzen EM Jr, Hamburg M, Hauer J, Henderson DA, Johnson RT, Kwik G, Layton M, Lillibridge S, Nabel GJ, Osterholm MT, Perl TM, Russell P, Tonat K; Working Group on Civilian Biodefense. Hemorrhagic fever viruses as biological weapons: medical and public health management. JAMA. 2002;287(18):2391-2405.

5 Monterey Institute for International Studies chemical and biological weapons resource page. Chemical and Biological Weapons. Monterey, Calif: Monterey Institute for International Studies; 2001. http://cns.miis.edu/cbw/cbw02_older.htm (Accessed 12/05/2012).

6 Jernigan DB, Raghunathan PL, Bell BP, Brechner R, Bresnitz EA, Butler JC, Cetron M, Cohen M, Doyle T, Fischer M, Greene C, Griffith KS, Guarner J, Hadler JL, Hayslett JA, Meyer R, Petersen LR, Phillips M, Pinner R, Popovic T, Quinn CP, Reefhuis J, Reissman D, Rosenstein N, Schuchat A, Shieh WJ, Siegal L, Swerdlow DL, Tenover FC, Traeger M,

Ward JW, Weisfuse I, Wiersma S, Yeskey K, Zaki S, Ashford DA, Perkins BA, Ostroff S, Hughes J, Fleming D, Koplan JP, Gerberding JL; National Anthrax Epidemiologic Investigation Team. Investigation of bioterrorism-related anthrax, United States, 2001: epidemiologic findings. Emerg Infect Dis. 2002 Oct;8(10):1019-28.

7 Shepard CW, Soriano-Gabarro M, Zell ER, Hayslett J, Lukacs S, Goldstein S, Factor S, Jones J, Ridzon R, Williams I, Rosenstein N; CDC Adverse Events Working Group. Antimicrobial postexposure prophylaxis for anthrax: adverse events and adherence. Emerg Infect Dis. 2002 Oct;8(10):1124-32.

8 Tierney BC, Martin SW, Franzke LH, Marano N, Reissman DB, Louchart RD, Goff JA, Rosenstein NE, Sever JL, McNeil MM; Centers for Disease Control and Prevention's Anthrax Vaccine and Antimicrobial Availability Program. Serious adverse events among participants in the Centers for Disease Control and Prevention's Anthrax Vaccine and Antimicrobial Availability Program for persons at risk for bioterrorism-related inhalational anthrax. Clin Infect Dis. 2003 Oct 1;37(7):905-11. Epub 2003 Sep 12.

9 Timmer SJ, Amundson DE, Malone JD. Hypersensitivity pneumonitis following anthrax vaccination. Chest. 2002 Aug;122(2):741-5.

10 Jefferds MD, Laserson K, Fry AM, Roy S, Hayslett J, Grummer-Strawn L, Kettel-Khan L, Schuchat A; Centers for Disease Control and Prevention Anthrax Adherence Team. Adherence to antimicrobial inhalational anthrax prophylaxis among postal workers, Washington, D.C., 2001. Emerg Infect Dis. 2002 Oct;8(10):1138-44.

11 Williams JL, Noviello SS, Griffith KS, Wurtzel H, Hamborsky J, Perz JF, Williams IT, Hadler JL, Swerdlow DL, Ridzon R. Anthrax postexposure prophylaxis in postal workers, Connecticut, 2001. Emerg Infect Dis. 2002 Oct;8(10):1133-7.

12 Partridge R, Alexander J, Lawrence T, Suner S. Medical counterbioterrorism: the response to provide anthrax prophylaxis to New York City US Postal Service employees. Ann Emerg Med. 2003 Apr;41(4):441-6.

13 Blank S, Moskin LC, Zucker JR. An ounce of prevention is a ton of work: mass antibiotic prophylaxis for anthrax, New York City, 2001. Emerg Infect Dis. 2003 Jun;9(6):615-22.

14 M'ikanatha NM, Julian KG, Kunselman AR, Aber RC, Rankin JT, Lautenbach E. Patients' request for and emergency physicians' prescription of antimicrobial prophylaxis for anthrax during the 2001 bioterrorism-related outbreak. BMC Public Health. 2005 Jan 5;5:2.

15 Center for Counterproliferation Research. Anthrax in America: A Chronology and Analysis of the Fall 2001 Attacks. http://www.ndu.edu/centercounter/ANTHRAX%20CHRONOLOGY.pdf (Accessed 8/09/2012).

16 Dougall AL, Hayward MC, Baum A. Media exposure to bioterrorism: stress and the anthrax attacks. Psychiatry. 2005 Spring;68(1):28-42.

17 Tengelsen L, Hudson R, Barnes S, Hahn C. Coordinated response to reports of possible anthrax contamination, Idaho, 2001. Emerg Infect Dis. 2002 Oct;8(10):1093-5.

18 Mott JA, Treadwell TA, Hennessy TW, Rosenberg PA, Wolfe MI, Brown CM, Butler JC. Call-tracking data and the public health response to bioterrorism-related anthrax. Emerg Infect Dis. 2002 Oct;8(10):1088-92.

19 Valiante DJ, Schill DP, Bresnitz EA, Burr GA, Mead KR. Responding to a bioterrorist attack: environmental investigation of anthrax in New Jersey. Appl Occup Environ Hyg. 2003 Oct;18(10):780-5.

20 Sanderson WT, Stoddard RR, Echt AS, Piacitelli CA, Kim D, Horan J, Davies MM, McCleery RE, Muller P, Schnorr TM, Ward EM, Hales TR. *Bacillus anthracis* contamination and inhalational anthrax in a mail processing and distribution center. J Appl Microbiol. 2004;96(5):1048-56.

21 Canter DA, Gunning D, Rodgers P, O'connor L, Traunero C, Kempter CJ. Remediation of *Bacillus anthracis* contamination in the U.S. Department of Justice mail facility. Biosecur Bioterror. 2005;3(2):119-27.

22 Mock M, Fouet A. Anthrax. Annu Rev Microbiol. 2001;55:647-71.

23 Liu H, Bergman NH, Thomason B, Shallom S, Hazen A, Crossno J, Rasko DA, Ravel J, Read TD, Peterson SN, Yates J 3rd, Hanna PC. Formation and composition of the *Bacillus anthracis* endospore. J Bacteriol. 2004 Jan;186(1):164-78.

24 Van Ness GB. Ecology of anthrax. Science. 1971 Jun 25;172(990):1303-7.

25 Dragon DC, Bader DE, Mitchell J, Woollen N. Natural dissemination of *Bacillus anthracis* spores in northern Canada. Appl Environ Microbiol. 2005 Mar;71(3):1610-5.

26 Dragon DC, Rennie RP. The ecology of anthrax spores: tough but not invincible. Can Vet J. 1995 May;36(5):295-301.

27 Osborn SH. Anthrax problem in Massachusetts. Am J Public Health (N Y). 1920 Aug;10(8):657-65.

28 Anonymous. Weekly Reports for March 10, 1911. Public Health Rep. 1911 March 10; 26(10): 277–312.

29 Anonymous. Weekly Reports for December 17, 1920. Public Health Rep. 1920 December 17; 35(51): 3007–3075.

30 Smyth HF, Cheney VS, Hubbard SD, Osborn SH. Industrial anthrax. Am J Public Health (NY). 1926 Jan;16(1):42-4.

31 Centers for Disease Control and Prevention. Summary of Notifiable Diseases, United States, 1998. MMWR Morb Mortal Wkly Rep. 1999 Dec 31;47(53):ii-92.

32 Cowan JA. Epidemiology of Anthrax in North Dakota. Am J Public Health Nations Health. 1940 Apr;30(4):411-6.

33 McNabb SJ, Jajosky RA, Hall-Baker PA, Adams DA, Sharp P, Anderson WJ, Javier AJ, Jones GJ, Nitschke DA, Worshams CA, Richard RA Jr; Centers for Disease Control and Prevention (CDC). Summary of notifiable diseases --- United States, 2005. MMWR Morb Mortal Wkly Rep. 2007 Mar 30;54(53):1-92.

34 Glassman HN. World incidence of anthrax in man. Public Health Rep. 1958 Jan;73(1):22-4.

35 Steele JH, Helvig RJ. Anthrax in the United States. Public Health Rep. 1953 Jun;68(6):616-23.

36 Bales ME, Dannenberg AL, Brachman PS, Kaufmann AF, Klatsky PC, Ashford DA. Epidemiologic response to anthrax outbreaks: field investigations, 1950-2001. Emerg Infect Dis. 2002 Oct;8(10):1163-74.

37 Smyth HF, Higgins WD. Report of the Committee on Industrial Anthrax (Anthrax in the United States, 1939-1943) : Industrial Hygiene Section. Am J Public Health Nations Health. 1945 Aug;35(8):850-8.

38 Smyth HF, Cheney VS. Anthrax as an Occupational Disease. Am J Public Health Nations Health. 1930 Feb;20(2):155-60.

39 Smyth HF. Anthrax-A Continuing and probably increasing hazard of industry. Am J Public Health (N Y). 1924 Nov;14(11):920-4.

40 Centers for Disease Control and Prevention, National Center for Health Statistics. Compressed Mortality File 1979-1998 Archive. CDC WONDER On-line Database, compiled from CMF 1968-1988, Series 20, No. 2A, 2000 and CMF 1989-2000, Series 20, No. 2C 2001. Accessed at http://wonder.cdc.gov/cmf-icd9-archive1998.html on Apr 20, 2008 6:05:16 PM

41 Centers for Disease Control and Prevention. Summary of notifiable diseases—United States, 2002. Published April 30, 2004, for MMWR 2002;51 (No. 53).

42 Hugh-Jones M. 1996-97 Global Anthrax Report. J Appl Microbiol. 1999 Aug;87(2):189-91.

43 Ozkurt Z, Parlak M, Tastan R, Dinler U, Saglam YS, Ozyurek SF. Anthrax in eastern Turkey, 1992-2004. Emerg Infect Dis. 2005 Dec;11(12):1939-41.

44 Peck RN, Fitzgerald DW. Cutaneous anthrax in the Artibonite Valley of Haiti: 1992-2002. Am J Trop Med Hyg. 2007 Nov;77(5):806-11.

45 Irmak H, Buzgan T, Karahocagil MK, Sakarya N, Akdeniz H, Caksen H, Demiröz P. Cutaneous manifestations of anthrax in Eastern Anatolia: a review of 39 cases. Acta Med Okayama. 2003 Oct;57(5):235-40.

46 Maguiña C, Flores Del Pozo J, Terashima A, Gotuzzo E, Guerra H, Vidal JE, Legua P, Solari L. Cutaneous anthrax in Lima, Peru: retrospective analysis of 71 cases, including four with a meningoencephalic complication. Rev Inst Med Trop Sao Paulo. 2005 Jan-Feb;47(1):25-30. Epub 2005 Feb 23.

47 Kanafani ZA, Ghossain A, Sharara AI, Hatem JM, Kanj SS. Endemic gastrointestinal anthrax in 1960s Lebanon: clinical manifestations and surgical findings. Emerg Infect Dis. 2003 May;9(5):520-5.

48 Anonymous. From the Centers for Disease Control and Prevention. Human ingestion of *Bacillus anthracis*-contaminated meat--Minnesota, August 2000. JAMA. 2000 Oct 4;284(13):1644-6.

49 Cole, ACE. Cutaneous Anthrax in Dar-es-Salaam. Br Med J. 1951 May 19; 1(4715): 1124.

50 Greenfield, W.S. Further Investigations on Anthrax and Allied Diseases in Man and Animals. Lancet. 1880. December 18th, 1880. pages 965-966.

51 Eurich, F.W. The History of Anthrax in the Wool Industry of Bradford and of Its Control. Lancet. January 2nd, 1926. 57-58, 107-109.

52 Laforce FM. Woolsorters' disease in England. Bull N Y Acad Med. 1978 Nov;54(10):956-63.

53 Legge, T.M. The Milroy Lectures on industrial anthrax: Delivered before the Royal College of Physicians of London. Br Med J. 1905 March 11; 1(2306): 529–531.

54 Legge, T.M. The Milroy Lectures on industrial anthrax: Delivered before the Royal College of Physicians of London. Br Med J. 1905 March 18; 1(2307): 589–593.

55 Legge, T.M. The Milroy Lectures on industrial anthrax: Delivered before the Royal College of Physicians of London. Br Med J. 1905 March 25; 1(2308): 641–643.

56 Eurich, F.W. Anthrax in the Woollen Industry, with Special Reference to Bradford. Proc R Soc Med. 1913; 6(Sect Epidemiol State Med): 219–240.

57 Smyth HF, Higgins WD. Report of the Committee on Industrial Anthrax (Check Anthrax-A Warning and a Plea) : Industrial Hygiene Section. Am J Public Health Nations Health. 1943 Jul;33(7):854-7.

58 Gold, H. Anthrax: A report of one hundred seventeen cases. Archives of Internal medicine. 1955;96:387-96.

59 Brown, W.H. and Simpson, C.E. Human anthrax. JAMA. 1917.LXVIII Number 8. pg 608-9.

60 Brachman PS, Plotkin SA, Bumford FH, Atchison MM. An epidemic of inhalation anthrax: the first in the twentieth century. II. Epidemiology. Am J Hyg. 1960 Jul;72:6-23.

61 Leake JP, Lederer A. Isolation of anthrax bacillus from shaving brushes. Am J Public Health (N Y). 1919 Feb;9(2):114-9.

62 Anonymous. Anthrax from shaving brushes. Am J Public Health (N Y). 1925 May;15(5):440.

63 National Health Service. Fatal case of anthrax. Press release. 2006. Aug 16. http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1253205582795 (Accessed 12/05/2012).

64 BBC News. Man dies from ‘rare anthrax bug’. 2006. Aug 16. http://newsvote.bbc.co.uk/mpapps/pagetools/print/news.bbc.co.uk/2/hi/uk_news/scotland/south_of_scotland/4797513.stm (Accessed 12/05/2012).

65 Centers for Disease Control and Prevention. Inhalation anthrax associated with dried animal hides--Pennsylvania and New York City, 2006. MMWR Morb Mortal Wkly Rep. 2006 Mar 17;55(10):280-2.

66 Walsh JJ, Pesik N, Quinn CP, et al. A case of naturally acquired inhalation anthrax: clinical care and analyses of anti-protective antigen immunoglobulin G and lethal factor. Clin Infect Dis. 2007 Apr 1;44(7):968-71. Epub 2007 Feb 26.

67 Centers for Disease Control and Prevention. Update on Inhalational Anthrax Investigation [press conference transcript]. 2006 Feb 22.

68 CNN. New York Man Falls Ill with Anthrax. 2006 Feb 22

69 Pennsylvania Department of Health. Anthrax Case Identified in PA [press release]. 2006 Feb 22

70 New York City Department of Health and Mental Hygiene. Inhalation Anthrax in a New York City Resident [press release]. 2006 Feb 22

71 Centers for Disease Control and Prevention. Inhalation Anthrax Case in Pennsylvania [Health Alert Network Advisory]. 2006 Feb 22

72 New York City Department of Health and Mental Hygiene. 3 neighbors receive antibiotics NYC [press release]. 2006 Feb 23

73 Chan, S. New York City Man Has Inhalation Anthrax. New York Times. 2006 Feb 23

74 New York City Department of Health and Mental Hygiene. Inhalation Anthrax in a New York City Resident Update [press release]. 2006 Feb 24

75 New York City Department of Health and Mental Hygiene. Inhalational Anthrax in a New York City Resident who works with Unprocessed Animal Hides [Veterinary Medical Alert]. 2006 Feb 24

76 Chan, S. A Wider Inquiry, as More People Get Antibiotics and 2nd Apartment Is to Be Checked. New York Times. 2006 Feb 24

77 Centers for Disease Control and Prevention. Inhalation Anthrax Case Investigation, Pennsylvania, NYC [Health Alert Network Advisory]. 2006 Feb 24

78 New York City Department of Health and Mental Hygiene. Crown Heights Residence Tests Negative for Anthrax [Press Release]. 2006 Feb 26

79 Brachman PS, Gold H, Plotkin SA, Fekety FR, Werrin M, Ingraham NR. Field Evaluation of a Human Anthrax Vaccine. Am J Public Health Nations Health. 1962 Apr;52(4):632-45.

80 Brachman PS, Gold H, Plotkin SA, Fekety FR, Werrin M, Ingraham NR. Field Evaluation of a Human Anthrax Vaccine. Am J Public Health Nations Health. 1962 Apr;52(4):632-45.

81 Advisory Committee on Immunization Practices. Use of anthrax vaccine in the United States. MMWR Recomm Rep. 2000 Dec 15;49(RR-15):1-20.

82 Code of Federal Regulations. Title 9 – Animals and Animal Products. Part 95 - Sanitary Control of Animal Byproducts (except casings), and Hay and Straw, Offered for Entry into the United States.

83 Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction, opened for signature at Washington, London, and Moscow April 10, 1972; entered into force March 26, 1975.

84 Gwertzman, B. Soviet Mishap Tied to Germ-War Plant. The New York Times. 1980 Mar 19.

85 Anonymous. Sverdlovsk Editor's Comment. The New York Times. 1980 Mar 21.

86 Gwertzman, B. Soviet Lays Outbreak of Illness to Bad Meat, Not Germ-War Plant. The New York Times. 1980 Mar 21.

87 Anonymous. Soviet Now Mentioning Foot and Mouth Disease. The New York Times. 1980 Mar 27.

88 Burt, R. New Reports on Soviet Anthrax Convince U.S. of Germ-War Tie. The New York Times. 1980 Mar 29.

89 Burt, R. U.S. Pressing Soviet on Reported Mishap with Germ Weapon. The New York Times. 1980 May 29.

90 Anonymous. Soviet Criticized on Germ Incident. The New York Times. 1980 Jun 29.

91 Anonymous. Toll Is Put at 1,000 in Soviet Accident. The New York Times. 1980 July 6.

92 Browne, M.W. Soviet Believed Equipped to Wage Chemical and Perhaps Biological War. The New York Times. 1980 Dec 8.

93 Wade N. Death at Sverdlovsk: a critical diagnosis. Science. 1980 Sep 26;209(4464):1501-2.

94 Meselson M, Guillemin J, Hugh-Jones M, et al. The Sverdlovsk anthrax outbreak of 1979. Science 1994; 266:1202-8.

95 Guillemin J. Anthrax: the investigation of a deadly outbreak. University of California Press. 2001.

96 Jackson PJ, Hugh-Jones ME, Adair DM, Green G, Hill KK, Kuske CR, Grinberg LM, Abramova FA, Keim P. PCR analysis of tissue samples from the 1979 Sverdlovsk anthrax victims: the presence of multiple *Bacillus anthracis* strains in different victims. Proc Natl Acad Sci U S A. 1998 Feb 3;95(3):1224-9.

97 Central Intelligence Agency. Regime Strategic Intent. Biological Warfare. [Report]. 2004.

98 U.S. Court of Appeals for Fifth Circuit. United States of America Versus Frank Paco Guevara. 16 May 2005.

99 US Court of Appeals for the Northern District of Florida. United States of America Versus Roger E. Evans. 16 Feb 2007.

100 Olson KB. Aum Shinrikyo: once and future threat? Emerg Infect Dis. 1999 Jul-Aug;5(4):513-6.

101 Takahashi H, Keim P, et al. *Bacillus anthracis* incident, Kameido, Tokyo, 1993. Emerg Infect Dis. 2004 Jan;10(1):117-20.

102 US District Court, District of Nevada. United States Versus Larry Wayne Harris, William Job Leavitt, Jr. 18 Feb 1998.

103 Federal Bureau of Investigation. Terrorism in the United States, 1998 [Report]. 1998.

104 Centers for Disease Control and Prevention. Syndromic surveillance for bioterrorism following the attacks on the World Trade Center--New York City, 2001. MMWR Morb Mortal Wkly Rep. 2002 Sep 11;51 Spec No:13-5.

105 Centers for Disease Control and Prevention. New York City Department of Health response to terrorist attack, September 11, 2001. MMWR Morb Mortal Wkly Rep. 2001 Sep 28;50(38):821-2.

106 Image from http://www.fbi.gov/about-us/history/famous-cases/anthrax-amerithrax/linguistic-behavorial-analysis-of-the-anthrax-letters (Accessed: 12/05/2012).

107 Federal Bureau of Investigation. Photos of Anthrax Letters to NBC, Senator Daschle, and NY Post. http://www.fbi.gov/pressrel/pressrel01/102301.htm (Accessed: 12/17/2009).

108 Hsu VP, Lukacs SL, Handzel T, Hayslett J, Harper S, Hales T, Semenova VA, Romero-Steiner S, Elie C, Quinn CP, Khabbaz R, Khan AS, Martin G, Eisold J, Schuchat A,

Hajjeh RA. Opening a *Bacillus anthracis*-containing envelope, Capitol Hill, Washington, D.C.: the public health response. Emerg Infect Dis. 2002 Oct;8(10):1039-43.

109 Sanderson WT, Stoddard RR, Echt AS, Piacitelli CA, Kim D, Horan J, Davies MM, McCleery RE, Muller P, Schnorr TM, Ward EM, Hales TR. *Bacillus anthracis* contamination and inhalational anthrax in a mail processing and distribution center. J Appl Microbiol. 2004;96(5):1048-56.

110 Centers for Disease Control and Prevention. Public Health Message Regarding Anthrax Case [Press Release]. 2001 Oct 04.

111 Florida Department of Health. Health officials investigating isolated and non-contagious case of anthrax [Press Release]. 2001 Oct 04.

112 Palm Beach County Health Department. Anthrax confirmed in Lantana Resident [Press Release]. 2001 Oct 04.

113 Ulferts, A., Ballingrud, D. "Terror or accidents? – Anthrax – CDC, FBI Investigate Lantana Case." St. Petersburg Times. 2001 Oct 05.

114 CNN. Florida man suffering from Anthrax Dies. http://archives.cnn.com/2001/HEALTH/conditions/10/05/anthrax.case. (Accessed 10/05/2001).

115 Albrink WS, Brooks SM, Biron RE, Kopel M. Human inhalation anthrax. A report of three fatal cases. Am J Pathol. 1960 Apr;36:457-71.

116 Dixon TC, Meselson M, Guillemin J, Hanna PC. Anthrax. N Engl J Med 1999; 341:815-26.

117 Drum CL, Yan SZ, Bard J, Shen YQ, Lu D, Soelaiman S, Grabarek Z, Bohm A, Tang WJ. Structural basis for the activation of anthrax adenylyl cyclase exotoxin by calmodulin. Nature. 2002 Jan 24;415(6870):396-402.

118 Hanna PC, Kochi S, Collier RJ. Biochemical and physiological changes induced by anthrax lethal toxin in J774 macrophage-like cells. Mol Biol Cell. 1992 Nov;3(11):1269-77.

119 Hanna PC, Acosta D, Collier RJ. On the role of macrophages in anthrax. Proc Natl Acad Sci U S A. 1993 Nov 1;90(21):10198-201.

120 Guidi-Rontani C, Weber-Levy M, Labruyère E, Mock M. Germination of *Bacillus anthracis* spores within alveolar macrophages. Mol Microbiol. 1999 Jan;31(1):9-17.

121 Gordon VM, Leppla SH, Hewlett EL. Inhibitors of receptor-mediated endocytosis block the entry of *Bacillus anthracis* adenylate cyclase toxin but not that of Bordetella pertussis adenylate cyclase toxin. Infect Immun. 1988 May;56(5):1066-9.

122 Dixon TC, Fadl AA, Koehler TM, Swanson JA, Hanna PC. Early *Bacillus anthracis*-macrophage interactions: intracellular survival survival and escape. Cell Microbiol. 2000 Dec;2(6):453-63.

123 Milne JC, Furlong D, Hanna PC, Wall JS, Collier RJ. Anthrax protective antigen forms oligomers during intoxication of mammalian cells. J Biol Chem. 1994 Aug 12;269(32):20607-12.

124 Petosa C, Collier RJ, Klimpel KR, Leppla SH, Liddington RC. Crystal structure of the anthrax toxin protective antigen. Nature. 1997 Feb 27;385(6619):833-8.

125 World Health Organization. Anthrax in Humans and Animals – 4th edition. 2008.

126 Vitale G, Pellizzari R, Recchi C, Napolitani G, Mock M, Montecucco C. Anthrax lethal factor cleaves the N-terminus of MAPKKS and induces tyrosine/threonine phosphorylation of MAPKS in cultured macrophages. J Appl Microbiol. 1999 Aug;87(2):288.

127 Pellizzari R, Guidi-Rontani C, Vitale G, Mock M, Montecucco C. Anthrax lethal factor cleaves MKK3 in macrophages and inhibits the LPS/IFNgamma-induced release of NO and TNFalpha. FEBS Lett. 1999 Nov 26;462(1-2):199-204.

128 Kirby JE. Anthrax lethal toxin induces human endothelial cell apoptosis. Infect Immun. 2004 Jan;72(1):430-9.

129 Green BD, Battisti L, Koehler TM, Thorne CB, Ivins BE. Demonstration of a capsule plasmid in *Bacillus anthracis*. Infect Immun. 1985 Aug;49(2):291-7.

130 Bradley KA, Mogridge J, Mourez M, Collier RJ, Young JA. Identification of the cellular receptor for anthrax toxin. Nature. 2001 Nov 8;414(6860):225-9.

131 Collier RJ, Young JA. Anthrax toxin. Annu Rev Cell Dev Biol. 2003;19:45-70.

132 Pezard C, Berche P, Mock M. Contribution of individual toxin components to virulence of *Bacillus anthracis*. Infect Immun. 1991 Oct;59(10):3472-7.

133 Friedlander AM. Macrophages are sensitive to anthrax lethal toxin through an acid-dependent process. J Biol Chem. 1986 Jun 5;261(16):7123-6.

134 Erwin JL, DaSilva LM, Bavari S, Little SF, Friedlander AM, Chanh TC. Macrophage-derived cell lines do not express proinflammatory cytokines after exposure to *Bacillus anthracis* lethal toxin. Infect Immun. 2001 Feb;69(2):1175-7.

135 Park JM, Greten FR, Li ZW, Karin M. Macrophage apoptosis by anthrax lethal factor through p38 MAP kinase inhibition. Science. 2002 Sep 20;297(5589):2048-51.

136 Mikesell P, Ivins BE, Ristroph JD, Dreier TM. Evidence for plasmid-mediated toxin production in *Bacillus anthracis*. Infect Immun. 1983 Jan;39(1):371-6.

137 Duesbery NS, Webb CP, Leppla SH, Gordon VM, Klimpel KR, Copeland TD, Ahn NG, Oskarsson MK, Fukasawa K, Paull KD, Vande Woude GF. Proteolytic inactivation of MAP-kinase-kinase by anthrax lethal factor. Science. 1998 May 1;280(5364):734-7.

138 Centers for Disease Control and Prevention. Case definitions for infectious conditions under public health surveillance. Centers for Disease Control and Prevention. MMWR Recomm Rep 1997; 46:1-55.

139 Bell DM, Kozarsky PE, Stephens DS. Clinical issues in the prophylaxis, diagnosis, and treatment of anthrax. Emerg Infect Dis 2002; 8:222-5.

140 Swartz MN. Recognition and management of anthrax--an update. N Engl J Med 2001; 345:1621-6.

141 Friedman HH. Problem-oriented medical diagnosis. Philadelphia, PA: Lippincott Williams & Wilkins, 2001:xv, 441.

142 Albrink WS, Brooks SM, Biron RE, Kopel M. Human inhalation anthrax. A report of three fatal cases. Am J Pathol. 1960 Apr;36:457-71.

143 Abramova FA, Grinberg LM, Yampolskaya OV, Walker DH. Pathology of inhalational anthrax in 42 cases from the Sverdlovsk outbreak of 1979. Proc Natl Acad Sci U S A 1993; 90:2291-4.

144 Grinberg LM, Abramova FA, Yampolskaya OV, Walker DH, Smith JH. Quantitative pathology of inhalational anthrax I: quantitative microscopic findings. Mod Pathol. 2001 May;14(5):482-95.

145 Inglesby TV, Henderson DA, Bartlett JG, et al. Anthrax as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. Jama 1999; 281:1735-45.

146 Centers for Disease Control and Prevention. Algorithm for Laboratory Diagnosis of Anthrax. http://www.bt.cdc.gov/agent/anthrax/lab-testing/algorithm.asp (Accessed 04/12/2008).

147 Centers for Disease Control and Prevention. Case definitions for infectious conditions under public health surveillance. MMWR Recomm Rep. 1997 May 2;46(RR-10):1-55.

148 Turnbull PC. Definitive identification of *Bacillus anthracis*--a review. J Appl Microbiol. 1999 Aug;87(2):237-40.

149 Plotkin SA, Brachman PS, Utell M, Bumford FH, Atchison MM. An epidemic of inhalation anthrax, the first in the twentieth century. I. Clinical features. Am J Med 1960; 29:992-1001.

150 LaForce FM, Bumford FH, Feeley JC, Stokes SL, Snow DB. Epidemiologic study of a fatal case of inhalation anthrax. Arch Environ Health 1969; 18:798-805.

151 Brachman PS, Pagano JS, Albrink WS. Two cases of fatal inhalation anthrax, one associated with sarcoidosis. N Engl J Med 1961; 265:203-208.

152 Suffin SC, Carnes WH, Kaufmann AF. Inhalation anthrax in a home craftsman. Hum Pathol 1978; 9:594-7.

153 Vessal K, Yeganehdoust J, Dutz W, Kohout E. Radiological changes in inhalation anthrax. A report of radiological and pathological correlation in two cases. Clin Radiol 1975; 26:471-4.

154 Centers for Disease Control and Prevention. Considerations for distinguishing influenza-like illness from inhalational anthrax. MMWR Morb Mortal Wkly Rep. 2001 Nov 9;50(44):984-6.

155 Kuehnert MJ et al. Clinical features that discriminate inhalational anthrax from other acute respiratory illnesses. Clin Infect Dis. 2003 Feb 1;36(3):328-36. Epub 2003 Jan 20.

156 Kyriacou DN, Stein AC, Yarnold PR, Courtney DM, Nelson RR, Noskin GA, Handler JA, Frerichs RR. Clinical predictors of bioterrorism-related inhalational anthrax. Lancet. 2004 Jul 31-Aug 6;364(9432):449-52.

157 Hupert N, Bearman GM, Mushlin AI, Callahan MA. Accuracy of screening for inhalational anthrax after a bioterrorist attack. Ann Intern Med. 2003 Sep 2;139(5 Pt 1):337-45.

158 Centers for Disease Control and Prevention. Flu Activity & Surveillance:

Reports & Surveillance Methods in the United States.

http://www.cdc.gov/flu/weekly/fluactivity.htm (Accessed 10/18/2007).

159 Kyriacou DN, Yarnold PR, Stein AC, Schmitt BP, Soltysik RC, Nelson RR, Frerichs RR, Noskin GA, Belknap SM, Bennett CL. Discriminating inhalational anthrax from community-acquired pneumonia using chest radiograph findings and a clinical algorithm. Chest. 2007 Feb;131(2):489-96.

160 Jernigan JA, Stephens DS, et al. Anthrax Bioterrorism Investigation Team. Bioterrorism-related inhalational anthrax: the first 10 cases reported in the United States. Emerg Infect Dis. 2001 Nov-Dec;7(6):933-44.

161 Cole, Leonard A. The Anthrax Letters: A Medical Detective Story. Joseph Henry Press. Washington, D.C. 2003.

162 Graysmith, Robert. Amerithrax: The Hunt for the Anthrax Killer. Berkeley Publishing Group. New York. 2003.

163 United States Department of Health and Human Services. Public Health Message Regarding Anthrax Case [Press Release]. 2001 Oct 04

164 Florida Department of Health. Death of Mr. Robert Stevens [Press Release]. 2001 Oct 05.

165 Kolata, G. "Florida Man is Hospitalized with Pulmonary Anthrax". New York Times. 2001 Oct 05

166 CNN. "Gupta: Isolated anthrax case extremely rare". http://archives.cnn.com/2001/HEALTH/conditions/10/05/gupta.otsc. (Accessed 12/05/2012).

167 Canedy, D., Wade, N. "Florida Man Dies of Rare Form of Anthrax". New York Times. 2001 Oct 06.

168 Ballingrud, D., Tisch, C. "Anthrax Fatality is likely isolated." St. Petersburg Times. 2001 Oct 06.

169 Tisch, C. "Single Anthrax Case Causes Few Ripples". St. Petersburg Times. 2001 Oct 06.

170 Centers for Disease Control and Prevention. Public Health Message Regarding Anthrax Case [Press Release]. 2001 Oct 07.

171 Florida Department of Health. Continuing Investigation [Press Release]. 2001 Oct 08.

172 CNN. Letter scrutinized as possible source. http://archives.cnn.com/2001/HEALTH/10/08/florida.anthrax.case/index.html (Accessed 12/05/2012).

173 Caldwell, A. "Tabloid workers tested for anthrax". St. Petersburg Times. 2001 Oct 08.

174 "What is anthrax?" St. Petersburg Times. 2001 Oct 09.

175 "Monday's development." St. Petersburg Times. 2001 Oct 09.

176 "Officials are on Alert." St. Petersburg Times. 2001 Oct 09.

177 "Police, hospitals heighten vigilance." St. Petersburg Times. 2001 Oct 09.

178 "Puzzle of Anthrax in Florida." New York Times. 2001 Oct 09.

179 Centers for Disease Control and Prevention. Public Health Message Regarding Anthrax Case [Press Release]. 2001 Oct 11.

180 Centers for Disease Control and Prevention. Public Health Message Regarding Anthrax Case [Press Release]. 2001 Oct 12.

181 Centers for Disease Control and Prevention. Anthrax Investigation, FL and NY [Press Release]. 2001 Oct 16.

182 Centers for Disease Control and Prevention. Update: Facts about anthrax testing and on-going investigations in Florida, Nevada, New York, and Washington, D.C. [Press Release]. 2001 Oct 17.

183 Centers for Disease Control and Prevention. Update: Anthrax antibiotic treatments and CDC disease detective status [Press Release]. 2001 Oct 17.

184 Centers for Disease Control and Prevention. Dr. Jeffrey P. Koplan, Director of CDC, answers important public health questions about anthrax [Video Conference Transcript]. 2001 Oct 18.

185 Centers for Disease Control and Prevention. Update: Investigation of anthrax associated with intentional exposure and interim public health guidelines, October 2001. MMWR Morb Mortal Wkly Rep. 2001 Oct 19;50(41):889-93.

186 Heymann, D.L. Control Of Communicable Diseases Manual. American Public Health Association; 18th edition. 2004.

187 Langmuir AD. The surveillance of communicable diseases of national importance. N Engl J Med 1963; 268:182-92.

188 North Carolina. Reportable diseases and conditions. (NCAC 41A .0101)

189 Minnesota Department of Health. http://health.minnesota.gov/divs/idepc/dtopics/reportable/forms/reptcard.html (Accessed 8/29/2009).

190 North Carolina. Method of Reporting. (NCAC 41A.0102)

191 Mostashari, FM, Hartman J. Syndromic surveillance: A local perspective. J Urban Health. 2003;80(2, suppl 1):i76–i88.

192 Henning KJ. What is syndromic surveillance? MMWR Morb Mortal Wkly Rep. 2004 Sep 24;53 Suppl:5-11.

193 Williams AA, Parashar UD, Stoica A, Ridzon R, Kirschke DL, Meyer RF, McClellan J, Fischer M, Nelson R, Cartter M, Hadler JL, Jernigan JA, Mast EE, Swerdlow DL;

Connecticut Anthrax Investigation Team. Bioterrorism-related anthrax surveillance, Connecticut, September-December, 2001. Emerg Infect Dis. 2002 Oct;8(10):1078-82.

194 Maillard JM, Fischer M, McKee KT Jr, Turner LF, Cline JS. First case of bioterrorism-related inhalational anthrax, Florida, 2001: North Carolina investigation. Emerg Infect Dis. 2002 Oct;8(10):1035-8.

195 Greene CM, Reefhuis J, et al. Epidemiologic investigations of bioterrorism-related anthrax, New Jersey, 2001. Emerg Infect Dis. 2002 Oct;8(10):1048-55.

196 Williams AA, Parashar UD, Stoica A, Ridzon R, Kirschke DL, Meyer RF, McClellan J, Fischer M, Nelson R, Cartter M, Hadler JL, Jernigan JA, Mast EE, Swerdlow DL; Connecticut Anthrax Investigation Team. Bioterrorism-related anthrax surveillance, Connecticut, September-December, 2001. Emerg Infect Dis. 2002 Oct;8(10):1078-82.

197 Buehler JW, Berkelman RL, Hartley DM, Peters CJ. Syndromic surveillance and bioterrorism-related epidemics. Emerg Infect Dis. 2003 Oct;9(10):1197-204.

198 Farrington CP, Andrews NJ, Beale AD, Catchpole MA. A Statistical Algorithm for the Early Detection of Outbreaks of Infectious Disease. Journal of the Royal Statistical Society. Series A (Statistics in Society) Vol. 159, No. 3 (1996), pp. 547-563

199 Proctor ME, Blair KA, Davis JP. Surveillance data for waterborne illness detection: an assessment following a massive waterborne outbreak of Cryptosporidium infection. Epidemiol Infect. 1998 Feb;120(1):43-54.

200 Lazarus R, Kleinman KP, Dashevsky I, DeMaria A, Platt R. Using automated medical records for rapid identification of illness syndromes (syndromic surveillance): the example of lower respiratory infection. BMC Public Health. 2001;1:9. Epub 2001 Oct 22.

201 Olson DR, Mostashari F. Distributed Surveillance Taskforce for Real-time Influenza Burden Tracking and Evaluation DiSTRIBuTE. http://www.syndromic.org/projects/Distribute_041108.ppt (Accessed 8/05/2011).

202 Plagianos MP, Soulakis ND. Syndromic Surveillance during Pandemic (H1N1) 2009 Outbreak, New York, New York, USA. Emerging Infectious Diseases. 2011.

203 Mandl KD, Overhage JM, Wagner MM, Lober WB, Sebastiani P, Mostashari F, Pavlin JA, Gesteland PH, Treadwell T, Koski E, Hutwagner L, Buckeridge DL, Aller RD, Grannis S. Implementing syndromic surveillance: a practical guide informed by the early experience. J Am Med Inform Assoc. 2004 Mar-Apr;11(2):141-50. Epub 2003 Nov 21.

204 Tsui FC, Espino JU, Dato VM, Gesteland PH, Hutman J, Wagner MM. Technical description of RODS: a real-time public health surveillance system. J Am Med Inform Assoc. 2003 Sep-Oct;10(5):399-408. Epub 2003 Jun 4.

205 Heffernan R, Mostashari F, Das D, Karpati A, Kulldorff M, Weiss D. Syndromic surveillance in public health practice, New York City. Emerg Infect Dis. 2004 May;10(5):858-64. Erratum in: Emerg Infect Dis. 2006 Sep;12(9):1472.

206 Gesteland PH, Gardner RM, Tsui FC, Espino JU, Rolfs RT, James BC, Chapman WW, Moore AW, Wagner MM. Automated syndromic surveillance for the 2002 Winter Olympics. J Am Med Inform Assoc. 2003 Nov-Dec;10(6):547-54. Epub 2003 Aug 4.

207 Meyer N, McMenamin J, Robertson C, Donaghy M, Allardice G, Cooper D. A multi-data source surveillance system to detect a bioterrorism attack during the G8 Summit in Scotland. Epidemiol Infect. 2008 Jul;136(7):876-85. Epub 2007 Aug 3.

208 Das D, Weiss D, Mostashari F, et al. Enhanced drop-in syndromic surveillance in New York City following September 11, 2001. J Urban Health 2003; 80:i76-88.

209 Vergu E, Grais RF, Sarter H, Fagot JP, Lambert B, Valleron AJ, Flahault A. Medication sales and syndromic surveillance, France. Emerg Infect Dis. 2006 Mar;12(3):416-21.

210 Goldenberg A, Shmueli G, Caruana RA, Fienberg SE. Early statistical detection of anthrax outbreaks by tracking over-the-counter medication sales. Proc Natl Acad Sci U S A. 2002 Apr 16;99(8):5237-40.

211 Cami A, Wallstrom GA, Fowlkes AL, Panozzo CA, Hogan WR. Mining aggregates of over-the-counter products for syndromic surveillance. Pattern Recognition Letters. 30 (2009) 255-266.

212 Hogan WR, Tsui FC, Ivanov O, Gesteland PH, Grannis S, Overhage JM, Robinson JM, Wagner MM; Indiana-Pennsylvania-Utah Collaboration. Detection of pediatric respiratory and diarrheal outbreaks from sales of over-the-counter electrolyte products. J Am Med Inform Assoc. 2003 Nov-Dec;10(6):555-62.

213 Besculides M, Heffernan R, Mostashari F, Weiss D. Evaluation of school absenteeism data for early outbreak detection, New York City. BMC Public Health. 2005 Oct 7;5:105

214 Cooper DL, Verlander NQ, Elliot AJ, Joseph CA, Smith GE. Can syndromic thresholds provide early warning of national influenza outbreaks? J Public Health (Oxf). 2009 Mar;31(1):17-25. Epub 2007 Nov 20.

215 Baker M, Smith GE, Cooper D, Verlander NQ, Chinemana F, Cotterill S, Hollyoak V, Griffiths R. Early warning and NHS Direct: a role in community surveillance? J Public Health Med. 2003 Dec;25(4):362-8.

216 Chapman WW, Christensen LM, Wagner MM, Haug PJ, Ivanov O, Dowling JN, Olszewski RT. Classifying free-text triage chief complaints into syndromic categories with natural language processing. Artif Intell Med. 2005 Jan;33(1):31-40.

217 Chapman WW, Dowling JN, Wagner MM. Classification of emergency department chief complaints into 7 syndromes: a retrospective analysis of 527,228 patients. Ann Emerg Med. 2005 Nov;46(5):445-55.

218 Fleischauer AT, Silk BJ, Schumacher M, Komatsu K, Santana S, Vaz V, Wolfe M, Hutwagner L, Cono J, Berkelman R, Treadwell T. The validity of chief complaint and discharge diagnosis in emergency department-based syndromic surveillance. Acad Emerg Med. 2004 Dec;11(12):1262-7.

219 Aronsky D, Kendall D, Merkley K, James BC, Haug PJ. A comprehensive set of coded chief complaints for the emergency department. Acad Emerg Med. 2001 Oct;8(10):980-9.

220 Mostashari F, Fine A, Das D, Adams J, Layton M. Use of ambulance dispatch data as an early warning system for communitywide influenzalike illness, New York City. J Urban Health. 2003 Jun;80(2 Suppl 1):i43-9.

221 Greenko J, Mostashari F, Fine A, Layton M. Clinical evaluation of the Emergency Medical Services (EMS) ambulance dispatch-based syndromic surveillance system, New York City. J Urban Health. 2003 Jun;80(2 Suppl 1):i50-6.

222 Hripcsak G, Soulakis ND, Li L, Morrison FP, Lai AM, Friedman C, Calman NS, Mostashari F. Syndromic surveillance using ambulatory electronic health records. J Am Med Inform Assoc. 2009 May-Jun;16(3):354-61. Epub 2009 Mar 4.

223 Brillman JC, Burr T, Forslund D, Joyce E, Picard R, Umland E. Modeling emergency department visit patterns for infectious disease complaints: results and application to disease surveillance. BMC Med Inform Decis Mak. 2005 Mar 2;5:4.

224 Craigmile PF, Kim N, Fernandez SA, Bonsu BK. Modeling and detection of respiratory-related outbreak signatures. BMC Med Inform Decis Mak. 2007 Oct 5;7:28.

225 Tsui FC, Wagner MM, Dato V, Chang CC. Value of ICD-9 coded chief complaints for detection of epidemics. Proc AMIA Symp. 2001:711-5.

226 Miller B, Kassenborg H, Dunsmuir W, Griffith J, Hadidi M, Nordin JD, Danila R. Syndromic surveillance for influenzalike illness in ambulatory care network. Emerg Infect Dis. 2004 Oct;10(10):1806-11.

227 Lewis MD, Pavlin JA, Mansfield JL, O'Brien S, Boomsma LG, Elbert Y, Kelley PW. Disease outbreak detection system using syndromic data in the greater Washington DC area. Am J Prev Med. 2002 Oct;23(3):180-6.

228 New York City Department of Health and Mental Hygiene Bureau of Communicable Disease. Chief Complaint Syndrome Coding Macro. http://www.syndromic.org/sas/NYCSyndromicMacros.sas (Accessed 08/08/2008).

229 Travers DA, Haas SW. Using nurses' natural language entries to build a concept-oriented terminology for patients' chief complaints in the emergency department. J Biomed Inform. 2003 Aug-Oct;36(4-5):260-70

230 Travers DA, Haas SW. Evaluation of emergency medical text processor, a system for cleaning chief complaint text data. Acad Emerg Med. 2004 Nov;11(11):1170-6.

231 New York City Department of Health and Mental Hygiene Bureau of Communicable Disease. Chief Complaint Syndrome Coding Macro. http://www.syndromic.org/sas/NYCSyndromicMacros.sas (Accessed 08/08/2008).

232 Centers for Disease Control and Prevention. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). http://www.cdc.gov/nchs/icd/icd9cm.htm (Accessed 12/05/2012).

233 Buckeridge DL, Okhmatovskaia A, Tu S, O'Connor M, Nyulas C, Musen MA. Understanding detection performance in public health surveillance: modeling aberrancy-detection algorithms. J Am Med Inform Assoc. 2008 Nov-Dec;15(6):760-9. Epub 2008 Aug 28.

234 Serfling, RE. Methods for Current Statistical Analysis of Excess Pneumonia-Influenza Deaths. Public Health reports. Vol. 78, No. 6, June 1963.

235 Wang L, Ramoni MF, Mandl KD, Sebastiani P. Factors affecting automated syndromic surveillance. Artif Intell Med. 2005 Jul;34(3):269-78.

236 Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ, Fukuda K. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA. 2003 Jan 8;289(2):179-86.

237 Wong CM, Chan KP, Hedley AJ, Peiris JS. Influenza-associated mortality in Hong Kong. Clin Infect Dis. 2004 Dec 1;39(11):1611-7. Epub 2004 Nov 10.

238 Hutwagner LC, Maloney EK, Bean NH, Slutsker L, Martin SM. Using laboratory-based surveillance data for prevention: an algorithm for detecting Salmonella outbreaks. Emerg Infect Dis. 1997 Jul-Sep;3(3):395-400.

239 Choi K, Thacker SB. An evaluation of influenza mortality surveillance, 1962-1979. I. Time series forecasts of expected pneumonia and influenza deaths. Am J Epidemiol. 1981 Mar;113(3):215-26.

240 Viboud C, Boëlle PY, Carrat F, Valleron AJ, Flahault A. Prediction of the spread of influenza epidemics by the method of analogues. Am J Epidemiol. 2003 Nov 15;158(10):996-1006.

241 Flamand C, Larrieu S, Couvy F, Jouves B, Josseran L, Filleul L. Validation of a syndromic surveillance system using a general practitioner house calls network, Bordeaux, France. Euro Surveill. 2008 Jun 19;13(25). pii: 18905.

242 Costagliola D, Flahault A, Galinec D, Garnerin P, Menares J, Valleron AJ. A routine tool for detection and assessment of epidemics of influenza-like syndromes in France. Am J Public Health. 1991 Jan;81(1):97-9.

243 Carrat F, Flahault A, Boussard E, Farran N, Dangoumau L, Valleron AJ. Surveillance of influenza-like illness in France. The example of the 1995/1996 epidemic. J Epidemiol Community Health. 1998 Apr;52 Suppl 1:32S-38S.

244 Reis BY, Mandl KD. Time series modeling for syndromic surveillance. BMC Med Inform Decis Mak. 2003 Jan 23;3:2. Epub 2003 Jan 23.

245 Wang L, Ramoni MF, Mandl KD, Sebastiani P. Factors affecting automated syndromic surveillance. Artif Intell Med. 2005 Jul;34(3):269-78.

246 Das D, Weiss D, Mostashari F, Treadwell T, McQuiston J, Hutwagner L, Karpati A, Bornschlegel K, Seeman M, Turcios R, Terebuh P, Curtis R, Heffernan R, Balter S.

Enhanced drop-in syndromic surveillance in New York City following September 11, 2001. J Urban Health. 2003 Jun;80(2 Suppl 1):i76-88.

247 Hutwagner L, Browne T, Seeman GM, Fleischauer AT. Comparing aberration detection methods with simulated data. Emerg Infect Dis. 2005 Feb;11(2):314-6.

248 Hutwagner LC, Thompson WW, Seeman GM, Treadwell T. A simulation model for assessing aberration detection methods used in public health surveillance for systems with limited baselines. Stat Med. 2005 Feb 28;24(4):543-50.

249 Tokars JI, Burkom H, Xing J, English R, Bloom S, Cox K, Pavlin JA. Enhancing time-series detection algorithms for automated biosurveillance. Emerg Infect Dis. 2009 Apr;15(4):533-9.

250 Lawson, A.B., Kleinman, K. Spatial and Syndromic Surveillance for Public Health.John Wiley and Sons. USA. 2005.

251 Reis BY, Pagano M, Mandl KD. Using temporal context to improve biosurveillance. Proc Natl Acad Sci U S A. 2003 Feb 18;100(4):1961-5. Epub 2003 Feb 6.

252 Reis BY, Mandl KD. Syndromic surveillance: the effects of syndrome grouping on model accuracy and outbreak detection. Ann Emerg Med. 2004 Sep;44(3):235-41.

253 Burkom HS. Development, adaptation, and assessment of alerting algorithms for biosurveillance. Johns Hopkins APL Technical Digest, 2003.

254 Brookmeyer, R., Stroup, D.F. Monitoring the health of populations: statistical principles and methods for public health surveillance. Oxford University Press US, 2004.

255 Fricker RD Jr, Hegler BL, Dunfee DA. Comparing syndromic surveillance detection methods: EARS' versus a CUSUM-based methodology. Stat Med. 2008 Jul 30;27(17):3407-29.

256 Hanslik T, Boelle PY, Flahault A. The control chart: an epidemiological tool for public health monitoring. Public Health. 2001 Jul;115(4):277-81.

257 Noble E, Johnson DW, Gray N, Hollett P, Hawley CM, Campbell SB, Mudge DW, Isbel NM. The impact of automated eGFR reporting and education on nephrology service referrals. Nephrol Dial Transplant. 2008 Dec;23(12):3845-50. Epub 2008 Jul 16.

258 Burkom HS, Murphy SP, Shmueli G. Automated time series forecasting for biosurveillance. Stat Med. 2007 Sep 30;26(22):4202-18.

259 Rogerson PA, Yamada I. Approaches to syndromic surveillance when data consist of small regional counts. MMWR Morb Mortal Wkly Rep. 2004 Sep 24;53 Suppl:79-85.

260 Buckeridge DL, Burkom H, Campbell M, Hogan WR, Moore AW. Algorithms for rapid outbreak detection: a research synthesis. J Biomed Inform. 2005 Apr;38(2):99-113.

261 Siegrist D, Pavlin J. Bio-ALIRT biosurveillance detection algorithm evaluation. MMWR Morb Mortal Wkly Rep. 2004 Sep 24;53 Suppl:152-8.

262 Betancourt JA, Hakre S, Polyak CS, Pavlin JA. Evaluation of ICD-9 codes for syndromic surveillance in the electronic surveillance system for the early notification of community-based epidemics. Mil Med. 2007 Apr;172(4):346-52.

263 Begier EM, Sockwell D, Branch LM, Davies-Cole JO, Jones LH, Edwards L, Casani JA, Blythe D. The National Capitol Region's Emergency Department syndromic surveillance

system: do chief complaint and discharge diagnosis yield different results? Emerg Infect Dis. 2003 Mar;9(3):393-6.

264 Beitel AJ, Olson KL, Reis BY, Mandl KD. Use of emergency department chief complaint and diagnostic codes for identifying respiratory illness in a pediatric population. Pediatr Emerg Care. 2004 Jun;20(6):355-60.

265 Marsden-Haug N, Foster VB, Gould PL, Elbert E, Wang H, Pavlin JA. Code-based syndromic surveillance for influenzalike illness by International Classification of Diseases, Ninth Revision. Emerg Infect Dis. 2007 Feb;13(2):207-16.

266 Behrendt CE. Acute respiratory failure in the United States: incidence and 31-day survival. Chest. 2000 Oct;118(4):1100-5.

267 Murphy SP, Burkom H. Recombinant temporal aberration detection algorithms for enhanced biosurveillance. J Am Med Inform Assoc. 2008 Jan-Feb;15(1):77-86. Epub 2007 Oct 18.

268 Jackson ML, Baer A, Painter I, Duchin J. A simulation study comparing aberration detection algorithms for syndromic surveillance. BMC Med Inform Decis Mak. 2007 Mar 1;7(1):6.

269 Zhu Y, Wang W, Atrubin D, Wu Y. Initial evaluation of the early aberration reporting system--Florida. MMWR Morb Mortal Wkly Rep. 2005 Aug 26;54 Suppl:123-30.

270 New York City Department of Health and Mental Hygiene. http://www.syndromic.org/sas/NYCSyndromicMacros.sas. (Accessed 10/7/2011).

271 Jernigan D.B. et al. Investigation of bioterrorism-related anthrax, United States, 2001: epidemiologic findings. Emerg Infect Dis. 2002 Oct;8(10):1019-28.

272 Behrendt CE. Acute respiratory failure in the United States: incidence and 31-day survival. Chest. 2000 Oct;118(4):1100-5.

273 International Classification of Diseases, 9th Edition. 1986.

274 Behrendt CE. Acute respiratory failure in the United States: incidence and 31-day survival. Chest. 2000 Oct;118(4):1100-5.

275 Dr. Lee H. Harrison, personal communication. 2001.

276 Chapman WW, Cooper GF, Hanbury P, Chapman BE, Harrison LH, Wagner MM. Creating a text classifier to detect radiology reports describing mediastinal findings associated with inhalational anthrax and other disorders. J Am Med Inform Assoc 2003; 10:494-503.

277 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

278 Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992; 45:613-9.

279 Barakat LA, Quentzel HL, Jernigan JA, et al. Fatal inhalational anthrax in a 94-year-old Connecticut woman. Jama 2002; 287:863-8.

280 Quintiliani R, Jr., Quintiliani R. Fatal case of inhalational anthrax mimicking intra-abdominal sepsis. Conn Med 2002; 66:261-7.

281 Mina B, Dym JP, Kuepper F, et al. Fatal inhalational anthrax with unknown source of exposure in a 61-year-old woman in New York City. Jama 2002; 287:858-62.

282 Mayer TA, Bersoff-Matcha S, Murphy C, et al. Clinical presentation of inhalational anthrax following bioterrorism exposure: report of 2 surviving patients. Jama 2001; 286:2549-53.

283 Bush LM, Abrams BH, Beall A, Johnson CC. Index case of fatal inhalational anthrax due to bioterrorism in the United States. N Engl J Med 2001; 345:1607-10.

284 Borio L, Frank D, Mani V, et al. Death due to bioterrorism-related inhalational anthrax: report of 2 patients. Jama 2001; 286:2554-9.

285 Sackett DL, Haynes RB, Tugwell P. Clinical epidemiology: a basic science for clinical medicine. Boston: Little Brown, 1985:xiii, 370 [1] of plates.

286 Simel DL, Samsa GP, Matchar DB. Likelihood ratios with confidence: sample size estimation for diagnostic test studies. J Clin Epidemiol 1991; 44:763-70.

287 Centers for Disease Control and Prevention BioSense. http://www.cdc.gov/biosense/ (Accessed 8/10/2012).

288 Dupont WD, Plummer WD: 'Power and Sample Size Calculations: A Review and Computer Program', Controlled Clinical Trials 1990; 11:116-28.

289 Tolliver, D. "What is the Variable Importance Measure?" http://www.salford-systems.com/blog/company/what-is-the-variable-importance-measure.html (Accessed 03/16/2012).

290 Luhr OR, Antonsen K, Karlsson M, Aardal S, Thorsteinsson A, Frostell CG, Bonde J., Incidence and mortality after acute respiratory failure and acute respiratory distress syndrome in Sweden, Denmark, and Iceland. The ARF Study Group.. Am J Respir Crit Care Med. 1999 Jun;159(6):1849-61.

291 Office of the National Coordinator for Health IT. Standards & Certification Criteria Final Rule. Published July 28, 2010. http://www.gpo.gov/fdsys/pkg/FR-2010-07-28/pdf/2010-17210.pdf (Accessed 04/12/2012).

292 Symonds, C. BMJ. April 25, 1885.

293 Browne, HL. BMJ. July 14, 1894.

294 Robinson, HB. Lancet. January 1, 1898.

295 Neave, EFM. Lancet. October 6th, 1900.

296 Clarke, EA. Lancet. November 10th, 1900.

297 Mutschler LH. A Report of Two Cases of Facial Anthrax Treated by Injections of Carbolic Acid, with Recovery. Ann Surg. 1901 Oct;34(4):555-9.

298 Kidd, A. Lancet. January 26th, 1901.

299 Wilson, RH. Lancet. October 12th, 1907.

300 Clarke, JS. Lancet. February 29th, 1908.

301 Roberts, TE. BMJ. April 18th, 1908.

302 Fallon, JC. California State Journal of Medicine. March, 1915.

303 Bennet, JA. Lancet. April 10th, 1915.

304 Snell. Lancet. January 29th, 1916.

305 Gilmour, CH. CMAJ. February, 1918.

306 Pernet, G. Case of Shaving-brush Anthrax of Face; Recovery. Proc R Soc Med. 1920; 13(Dermatol Sect): 25–26.

307 Rankin, AL. Lancet. February 21st, 1931.

308 Hunt, MF. BMJ. January 8th, 1955.

309 Centers for Disease Control and Prevention. Human cutaneous anthrax--North Carolina, 1987. MMWR Morb Mortal Wkly Rep. 1988 Jul 8;37(26):413-4.

310 Taylor JP, Dimmitt DC, Ezzell JW, Whitford H. Indigenous human cutaneous anthrax in Texas. South Med J. 1993 Jan;86(1):1-4.

311 Smego RA Jr, Gebrian B, Desmangels G. Cutaneous manifestations of anthrax in rural Haiti. Clin Infect Dis. 1998 Jan;26(1):97-102.

312 World Health Organization. Weekly Epidemiological Record. August 23rd, 1991.

313 de Lalla F, Ezzell JW, Pellizzer G, et al. Familial outbreak of agriculture anthrax in an area of northern Italy. Eur J Clin Microbiol Infect Dis 1992;11:839-842.

314 Natori N. A case of cutaneous anthrax. Tohoku J Exp Med. 1995 Jul;176(3):187-90.

315 Mallon E, McKee PH. Extraordinary case report: cutaneous anthrax. Am J Dermatopathol. 1997 Feb;19(1):79-82.

316 Centers for Disease Control and Prevention. Human anthrax associated with an epizootic among livestock--North Dakota, 2000. MMWR Morb Mortal Wkly Rep. 2001 Aug 17;50(32):677-80.

317 Freedman A, Afonja O, Chang MW, Mostashari F, Blaser M, Perez-Perez G, Lazarus H, Schacht R, Guttenberg J, Traister M, Borkowsky W. JAMA. 2002 Feb 20;287(7):869-74.

318 Centers for Disease Control and Prevention. Update: Cutaneous anthrax in a laboratory worker--Texas, 2002. MMWR Morb Mortal Wkly Rep. 2002 Jun 7;51(22):482.

319 Bell JH. On “Woolsorter's disease”. Lancet 1880; 115:871-873.

320 Bell JH. On “Woolsorter's disease”. Lancet 1880; 115:903-940.

321 Bell JH. Woolsorter's disease at Bradford. Lancet 1880; 115:819-821.

322 Bell JH. Woolsorters' disease. British Medical Journal 1881:101.

323 Bell JH. On Woolsorters' disease. British Medical Journal 1881:915-916.

324 Wilmot T. Woolsorters' disease. British Medical Journal 1883.

325 Tunstall AE. A case of wool-sorters' disease. Lancet 1897; 149:377.

326 Severn M. A fatal case of pulmonary anthrax. Br Med J. 1976 Mar 27;1(6012):748.

327 Dutz W, Saidi F, Kohout E. Gastric anthrax with massive ascites. Gut. 1970 Apr;11(4):352-4

328 Alizad A, Ayoub EM, Makki N. Intestinal anthrax in a two-year-old child. Pediatr Infect Dis J. 1995 May;14(5):394-5.

329 Tekin A, Bulut N, Unal T. Acute abdomen due to anthrax. Br J Surg. 1997 Jun;84(6):813.

330 Tabatabaie P, Syadati A. *Bacillus anthracis* as a cause of bacterial meningitis. Pediatr Infect Dis J. 1993 Dec;12(12):1035-7.

331 Yorgancigil B, Demirci M, Unlu M, Sevük E, Doganay M. Anthrax meningitis: case report. Int J Infect Dis. 2001;5(4):220-1.

332 Kwong KL, Que TL, Wong SN, So KT. Fatal meningoencephalitis due to *Bacillus anthracis*. J Paediatr Child Health. 1997 Dec;33(6):539-41.