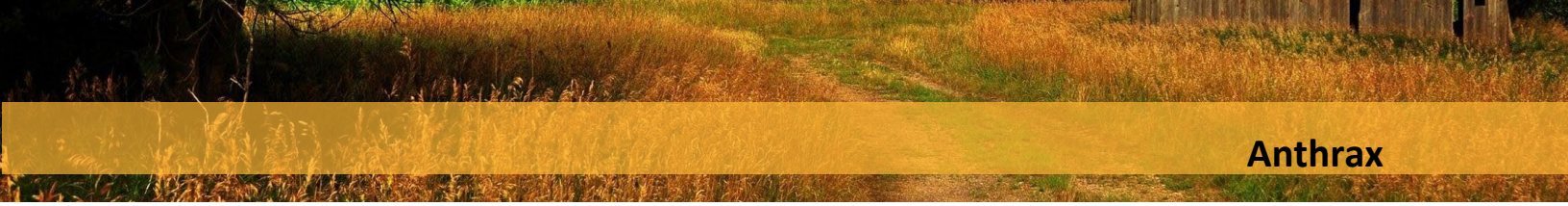

Anthrax

Anthrax is a zoonotic disease that most commonly affects domestic and wild herbivores[1-3]. Animals such as cattle, sheep, goats, antelope, and deer can become infected after being exposed to contaminated soil, plants, or water[3]. Contact with anthrax can cause severe illness in both humans and animals[3]. Anthrax has not been identified in the environment, animals, or humans in Arizona's history.

A. Agent:

Anthrax is an infectious disease caused by the bacteria *Bacillus anthracis*, a gram-positive, spore-forming, non-motile rod[1-3]. The spores, specifically, of *B. anthracis* are the infectious form[2]. Spores can remain viable in soil for decades and pose a continuous potential source of infection, particularly for herbivores eating off of the contaminated soil[1-3]. The spores can also contaminate animal fur, pelts, and meat[1-3]. *B. anthracis* has three virulence factors: an antiphagocytic capsule, lethal toxin, and edema toxin[1-2]. These toxins are responsible for the clinical manifestations, including hemorrhage, edema, and necrosis[1].

B. Clinical Description:

Anthrax is a serious life threatening disease and clinical presentation varies according to route of infection[1-3]. All routes of infection may lead to hemorrhagic meningitis, even in the absence of other symptoms, with a case fatality rate approaching 100%[1-3]. There are four main routes of infection[1-3]:

Cutaneous Anthrax –Cutaneous anthrax represents over 95% of naturally acquired human cases and begins with a group of small, itchy blisters or a pruritic papule that enlarges and ulcerates in 1 or 2 days, leading to the formation of a central black eschar[1-4]. This lesion is characteristically painless, with surrounding edema and hyperemia[1-3]. The eschar is most commonly found on the face, neck, arms or hands because these are the areas most likely to come into contact with the contaminated material[1-4]. Upon treatment, the case fatality rate is less than 1%[1-4].

- Differential Diagnosis: May present similarly to bacterial furunculosis, orf (ecthyma contagiosum) or a brown recluse spider bite[2,4]. Anthrax can be distinguished from these as the only one with a characteristically painless lesion and associated edema[2,4].

Ingestion anthrax: presents as two sub-types:
(1) Oropharyngeal: When anthrax spores germinate in the oropharynx, a mucosal lesion may be observed in the oral cavity or oropharynx. Symptoms include sore throat, difficulty swallowing, and swelling of the neck. Less specific symptoms include fever, fatigue, shortness of breath, abdominal pain, and nausea/vomiting; the symptoms may resemble a viral respiratory illness. Cervical lymphadenopathy, ascites, and altered mental status may be observed.
(2) Gastrointestinal: When anthrax spores germinate in the lower gastrointestinal tract, symptoms include abdominal pain, nausea, vomiting or diarrhea (either of which may contain blood), and abdominal swelling. Less specific symptoms such as fever, fatigue,

Inhalation Anthrax – Inhalation anthrax is often lethal and should be treated as a medical emergency[1-2, 4]. It typically starts with a nonspecific prodrome which includes fever, chills, chest pain, headache, myalgia, malaise, nausea, shortness of breath and body aches[1-4]. Occasionally a period of recovery occurs between the prodrome and the fulminant phase of the illness, which occurs 2 to 5 days later[1-2,4]. Fulminant manifestations include hypotension, dyspnea, hypoxia, and cyanosis[1-2,4]. Shock may result from hemorrhagic pneumonia, hemorrhagic pleural effusions, bacteremia, and toxemia[1-2,4]. A widening of the mediastinum is a classical finding upon imaging of the chest[1-2.,4]. Case fatality rates can exceed 85%, but early diagnosis and aggressive antimicrobial therapy and supportive care can decrease fatality rates to approximately 55%[1-3].

- Differential Diagnosis: May present similarly to influenza, but can be distinguished by the presence of a widening mediastinum on chest radiography, or culture results[1-2,4]. Also presents similarly to

Mycoplasma pneumonia or viral pneumonia, but can be distinguished by the presence of *B. anthracis* in blood culture[1-2,4]. May present similarly to Bronchitis, but with several severe additional symptoms including loss of consciousness, confusion, nausea, and vomiting[1-2,4]. May also present similarly to cardiac syndromes, such as a ruptured aortic artery or superior vena cava syndrome[1-2,4]. Anthrax can be distinguished if the mediastinal changes occur early in infection along with pulmonary edema[1-2,4].

Injection Anthrax **–** Injection anthrax has been identified among heroin-injecting drug users in Northern Europe[1-3]. Injection anthrax presents with symptoms similar to cutaneous anthrax but often includes serious localized soft tissue infection and significant edema[1-4]. Systemic infection, including hemorrhagic meningitis and multiorgan failure, can occur[1-4]. A case-fatality rate of over 20% has been observed with injection anthrax cases[2].

- Differential Diagnosis: May present similarly to necrotizing fasciitis, cellulitis, or abscess but is less likely to present with fever and pain is often less severe[1-2]. Injection anthrax can also be distinguished through blood cultures[1-2].

Additional considerations:
1) Signs of systemic involvement from the dissemination of either the bacteria and/or its toxins can occur with all types of anthrax and include fever or hypothermia, tachycardia, tachypnea, hypotension, and leukocytosis. One or more of these signs are usually present in patients with ingestion anthrax, inhalation anthrax, and injection anthrax and may be present in up to a third of patients with cutaneous anthrax.
2) Anthrax meningitis: may complicate any form of anthrax, and may also be a primary manifestation. Primary symptoms include fever, headache (which is often described as severe), nausea, vomiting, and fatigue. Meningeal signs (e.g., meningismus), altered mental status, and other neurological signs such as seizures or focal signs are usually present. Most patients with anthrax meningitis have CSF abnormalities consistent with bacterial meningitis, and the CSF is often described as hemorrhagic.

C. Reservoirs:

Infected animals may act as a source of exposure for anthrax infection, but they are not necessary[1-3]. An additional source of infection is soil or fomites contaminated with spores[1-3].

D. Mode of Transmission:

Transmission can occur by four different routes; inhalation, ingestion, cutaneous, and, in rare instances, injection[1-3].

Cutaneous Anthrax - occurs when people handle contaminated materials[1-3].

Inhalation Anthrax **-** occurs when people inhale spores that are in the air, historically during the industrial processing of contaminated animal materials such as wool, hides, or hair[1-3]. In the 2001 U.S. anthrax attacks, the spores were combined with a white powder to be inhaled upon opening the envelope that contained them[1-3].

Ingestion Anthrax **-** occurs when people eat raw or undercooked meat from an infected animal[1-3].

Injection Anthrax - is a newly recognized route of infection seen in heroin users in northern Europe. So far this has not been seen in the United States[1-3].

Anthrax is not contagious between people, although atypical incidents of cutaneous transmission from one person to another via discharges from skin lesions have been documented[1-3].

E. Incubation Period:

Cutaneous and Ingestion Anthrax - both have an incubation period of 1 week or less[1-4].

Inhalation Anthrax - has an incubation period of anywhere from 1 to 43 days, and up to 2 months in experimental models[1-4]. This is due to an extended period of spore dormancy in the lungs and slow spore clearance[1].

Injection Anthrax - has an incubation period of 1-10 days[1-4].

F. Period of Communicability:

Anthrax is not contagious between people, although atypical incidents of cutaneous transmission from one person to another via discharges from skin lesions have been documented[1-3].

G. Susceptibility and Resistance:

Antibiotics, specifically ciprofloxacin and doxycycline, can prevent anthrax from developing in people who have been exposed but not developed symptoms[1-3]. Following exposure it can take spores up to 60 days to activate in the human host, therefore antibiotics must be taken for at least 60 continuous days[1-3]. The Anthrax Vaccine Absorbed (AVA) is a licensed vaccine for cutaneous and inhalation anthrax approved by the FDA[1-3]. It is not given to the general public, but only to those at risk of exposure such as laboratory or animal workers or those in the military[1-3]. AVA should be given in 5 doses over a period of 18 months and are injected intramuscularly[1-3]. In certain situations, such as a bioterrorism attack, AVA can also be given to previously unvaccinated individuals who have been exposed to anthrax; these individuals should be given 3 doses of subcutaneous vaccine as soon after exposure as possible, and then at 2 and 4 weeks post exposure[1-3]. In post-exposure instances, AVA should be administered in addition to a 60 day course of antibiotics[1-2]. The vaccine should not be given to anyone who has had a previous allergic reaction to the anthrax vaccine or any component of it, or pregnant women (except in emergency situations, such as a bioterrorism attack)[2].

H. Treatment:

Following exposure, if someone has symptoms of anthrax it is important to get immediate medical treatment[1-3]. Due to limited clinical experience and a lack of controlled trials in humans, most evidence is based on previous case reports[1]. Case reports suggest that naturally occurring cutaneous anthrax disease can be successfully treated with a number of antimicrobial agents, including but not limited to, penicillin and tetracycline for 7 to 10 days[1]. Bioterrorism associated cutaneous anthrax should be treated with ciprofloxacin, 30 mg/kg per twice per day orally, divided to twice a day for children, not to exceed 1000 mg every 24 hours[1]. Another option is doxycycline 100 mg orally, divided two times a day for children under 8 years, or 4.4 mg/kg per day orally, divided twice a day for children under 8 years[1]. A multi-drug approach is preferred if there are signs of systemic disease, extensive edema, or lesions to the head and neck[1-2].

Animal studies suggest that ciprofloxacin, 400 mg intravenously every 8–12 hours, is recommended as the initial therapy in a multi-drug approach for inhalation anthrax, anthrax meningitis, systemic cutaneous anthrax, or gastrointestinal anthrax[1]. Meningitis treatment must also include an agent capable of penetrating the central nervous system (CNS), and should always be suspected in cases of inhalation or systemic anthrax infections[1]. In addition, one to two other agents with CNS penetrating abilities are recommended[1]. Cephalosporins and trimethoprim-sulfamethoxazole should not be used to treat anthrax due to intrinsic resistance[1]. Due to the risk of spore dormancy, treatment should always be continued for 60 days[1-4].

Additional treatment guidelines for healthcare professionals, including antitoxin treatments and other special considerations, can be found at https://www.cdc.gov/anthrax/healthcare/index.html

Disease Management

I. Clinical Criteria:

For surveillance purposes, an illness with at least one specific OR two non-specific symptoms and signs that are compatible with cutaneous, ingestion, inhalation, or injection anthrax (refer to section B. of this protocol); systemic involvement; or anthrax meningitis; OR
A death of unknown cause AND organ involvement consistent with anthrax.[5-6]

J. Laboratory Criteria for Diagnosis:

Confirmatory laboratory criteria for *Bacillus anthracis* or *Bacillus cereus* expressing anthrax toxins:

- Culture and identification from clinical specimens by Laboratory Response Network (LRN);
- Demonstration of *B. anthracis* antigens in tissues by immunohistochemical staining using both *B. anthracis* cell wall and capsule monoclonal antibodies;
- Evidence of a four-fold rise in antibodies to protective antigen between acute and convalescent sera or a fourfold change in antibodies to protective antigen in paired convalescent sera using Centers for Disease Control and Prevention (CDC) quantitative anti-PA IgG ELISA testing in an unvaccinated person;
- Detection of *B. anthracis* or anthrax toxin genes by the LRN-validated polymerase chain reaction and/ or sequencing in clinical specimens collected from a normally sterile site (such as blood or CSF) or lesion of other affected tissue (skin, pulmonary, reticuloendothelial, or gastrointestinal);
- Detection of lethal factor (LF) in clinical serum specimens by LF mass spectrometry.

Presumptive laboratory criteria for *Bacillus anthracis* or *Bacillus cereus* expressing anthrax toxins:

- Gram stain demonstrating Gram-positive rods, square-ended, in pairs or short chains;
- Positive result on a test with established performance in a CLIA-accredited laboratory.

Epidemiologic Linkage

- Exposure to environment, food, animal, materials, or objects that is suspect or confirmed to be contaminated with *B. anthracis*;
- Exposure to the same environment, food, animal, materials, or objects as another person who has laboratory-confirmed anthrax;
- Consumption of the same food as another person who has laboratory-confirmed anthrax.

Case Classification[5-6]	
Confirmed	● A case that meets the clinical criteria AND has confirmatory laboratory results
Probable	● A case that meets the clinical criteria AND has presumptive laboratory results, OR ● A case that meets the clinical criteria AND has epidemiologic evidence relating it to anthrax.
Suspect	A case that meets the clinical criteria AND for whom an anthrax test was ordered, but with no epidemiologic evidence relating it to anthrax.

K. Classification of Import Status:

A case is considered imported if the person became infected outside of the U.S. This should be considered when there is opportunity for exposure and epidemiological evidence more suggestive of infection elsewhere. A case may also be imported from one state into another, or one local jurisdiction into another. All opportunities for exposure and epidemiological evidence should be documented for assessment of import status. If exposure is thought to have occurred in Mexico/Canada, mark as *bi-national* in MEDSIS.

L. Laboratory Testing[3,7]:

Collect both a serology and culture to be sent to the Arizona State Public Health Lab for testing.

DISEASE	SPECIMEN	COLLECTION
Cutaneous Anthrax	Sterile swabs to collect vesicular fluid and eschar material[7].	Vesicular fluid should be obtained from a previously unopened vesicle using a sterile swab[7]. To collect eschar material, carefully lifting the eschar's outer edge, insert a sterile swab and slowly rotate for 2-3 seconds beneath the edge of the eschar without removing it[7]. Place the swab in the appropriate transport container and ship at 2-8°C[7].
Inhalation or GI Anthrax	Collect blood, serum, plasma, pleural fluid, transtracheal aspirates, sputum, fresh or frozen tissue, stool or rectal swab[7].	Place the swab or specimen in the appropriate transport container and ship at 2-8°C[7].

TEST	SPECIMEN	TRANSPORT MEDIA	RESULTS
PCR	Blood, serum, Isolate (liquid or plated), plasma, pleural fluid, transtracheal aspirate, sputum, tissue[7].	Blood samples must be submitted in tubes with EDTA[7].	4 days[7]
Culture	Vesicular fluid, swab of eschar material, blood, sputum, stool[7].	Standard bacterial transport media[7].	4 days[7]

M. Assessing Laboratory Results:

Cultures will be incubated for 72 hours and checked daily for macroscopic morphology[7]. Suspected isolates are tested biochemically and by Real-Time PCR[7]. Confirmation is made using Laboratory Response Network (LRN) protocols and algorithms[7]. Once a Bacillus isolate has been confirmed as negative for anthrax, any further identification will require approval from the Technical Supervisor[7].

All results, positive or negative will be phoned to the submitting agencies and when appropriate, reported to ADHS OIDS and local and federal law enforcement[7].

N. Outbreak Definition:

Outbreaks of anthrax infection have been known to occur in livestock, which puts humans at a higher level of risk[1-3]. Outbreaks in industrialized nations have also been associated with professions that directly handle animal material, especially goat hair[1-3]. There have also been outbreaks associated with consuming and handling undercooked contaminated cattle products[1-3]. Due to the rarity of infections, an unexplained, unexpected increase in anthrax

cases that is clustered by time, place, or person should be considered a potential outbreak scenario.

O. Time Frame:[8]

Providers must submit a report to the Local Health Department by telephone or through an electronic reporting system authorized by ADHS within 24 hours after a case or suspect case is diagnosed, treated, or detected or an occurrence is detected. Laboratories must submit a report to ADHS immediately after receiving 1 specimen for detection of the agent and report receipt of subsequent specimens within 5 working days after receipt. Laboratories must submit a report to ADHS within 24 hours after obtaining a positive test result. Laboratories must submit an isolate of the organism for each positive culture to ASPHL at least once each week, as applicable.

P. Forms:

- ADHS Anthrax Disease Investigation Form:

Q. Investigation Steps:

- **Confirm Diagnosis**
  i. Before contacting the patient or family, determine what information is available from medical records, physician, etc.
  ii. Obtain information that supports clinical findings, including:
    - Eschar (date of onset, duration and presentation), date of onset of each symptom, complications, hospitalizations, and outcome status (survived or date of death).
    - For hospitalizations, obtain medical records, including admission notes, progress notes, lab reports, and discharge summary.
  iii. Obtain information on any laboratory tests performed and results or date results are expected.
    - If laboratory tests have not been run to test for *B. anthracis* coordinate testing to confirm the case.
    - If cultures or PCR need to be performed, testing should be coordinated with ADHS.
  iv. Make a note of the laboratory (location and contact information) performing any tests and the expected turn-around time for testing.
    - ASPHL turnaround time for *B. anthracis* results is 4 days.

- **Conduct Case Investigation**
  REMEMBER: Case investigation and vaccination of susceptible contacts should not be delayed pending laboratory results.
  i. Collect information as specified on the Communicable Disease Report. Also collect the following information:
    - Birth date, county, sex, race/ethnicity, dates of exposure, reason for infection (e.g. animal contact, relationship to a case, etc.), and occupation.
    - Resident of your county? If not, determine if the case is an international import or an out-of-state import.
    - Travel history:
      - Dates of exit from and reentry to Arizona
      - Locations (include dates of locations traveled)
  ii. Focus on an incubation period of 1 week or less, but remember that it may be greater if inhalation is the suspected route of infection.
  iii. Keep in mind that anthrax is considered a Tier 1 agent, meaning there is a high likelihood of deliberate misuse. Deliberate misuse should be considered under the following circumstances:

- Failure to identify a likely epidemiological explanation for exposure
- Unusually high morbidity or mortality
- An unusually virulent or pathogenic strain of a pathogen
- A disease occurrence in a non-endemic area, plus no travel history to an endemic area

iv. Collect information on the following:
- Any visits to a doctor's office, clinic, or hospital (exact date and time)
- Any outdoor events, work conditions, or hobbies that would bring cases into contact with infected animals

▪ **Conduct Contact Investigation**

i. Determine if the case is involved in a high-risk occupation or if another special situation is involved.
ii. Susceptible contacts are anyone who came into contact with the same exposure source as the first patient.
iii. All potentially exposed individuals should be provided with post-exposure prophylaxis and assessed by a clinician.

▪ **Initiate Control and Prevention Measures**

Anthrax is essentially non-contagious[1-3]. Therefore, efforts should focus on recognizing symptoms, treating those exposed, sterilizing the exposure source, and investigating the potential for bioterror threats, when applicable[1-3].

Additional preventative and non-pharmaceutical interventions include:
- Vaccinating livestock in areas where anthrax is endemic[1-3].
- Doxycycline and Ciprofloxacin for Post-exposure Prophylaxis (PEP) of Anthrax https://www.cdc.gov/anthrax/medical-care/emergency-use-doxycycline-ciprofloxacin.html
- The AVA vaccine should be administered to anyone working in a high risk environment, such as, veterinarians, those in the military, and any workers who are exposed to raw animal materials.
- In the case of potential human exposure, individuals should be given the AVA vaccine as PEP[1-3].
- Educating workers of high risk industries, such as leather tanners[1-3].
- Ensuring that hazardous work areas are properly ventilated[1-3].
- Ensuring hazardous materials (including any material of animal origins) are disinfected or sterilized[1-3].
- Any materials known to be contaminated should be destroyed[1-3].
- Spores can survive for decades in the environment, so carcasses should not be necropsied following death[1-3]. Instead, aseptically collect a blood sample for smear or culture[1-3]. If a necropsy does occur, all biological materials and contaminated instruments should be autoclaved as soon as possible[1-3].
  - If autoclaving is not possible, the contaminated materials should be buried as deeply as possible in the soil while remaining above the waterline. Lye and quicklime should **not** be applied[1-3].

▪ **Notifications**

i. Notify program manager immediately. (If local jurisdiction, report all cases by telephone to ADHS within 24 hours of initial report)
ii. If there are cases involving livestock, alert the Department of Agriculture, Office of the State Veterinarian (602-542-4373)/diseasereporting@azda.gov.
iii. Encourage the consideration of an anthrax infection diagnosis in those fitting the clinical case definition and make clinicians and public health officials aware of differential diagnoses. Emphasize the need to report all suspected cases immediately.
iv. As appropriate, notify the case, contacts, and other individuals or groups.

R. Outbreak Guidelines:

Refer to the Outbreak Section of the Disease Investigation Manual.

S. Special Situations:

Bioterrorism Risk

Anthrax is designated as a Tier 1 biological agent because it represents a great risk of deliberate misuse with significant potential for devastating effects to the economy, infrastructure and healthcare[3]. Anthrax spores are easily found in nature, can be produced in a lab, and can last in the environment for extended periods of time[3]. It can also be released quietly and without anyone knowing[3]. The spores can be put into powders, sprays, food, and water[3]. The most significant method of dispersal for a biological weapon would be aerosolized[3].

Any investigations involving anthrax infection should document the signs of a potential intentional release of a pathogen—when applicable[2-3]:

- Failure to identify a likely epidemiological explanation for exposure[2-3]
- Unusually high morbidity or mortality[2-3]
- An unusually virulent or pathogenic strain of a pathogen[2-3]
- A disease occurrence in a non-endemic area, plus no travel history to an endemic area[2-3]

Control Measures for a Potential Bioterror Event:

Health departments should implement plans for educating and reminding healthcare providers how to recognize and diagnose anthrax infection[2-3]. Potential bioterror agents are often non-endemic, or rarely seen, and healthcare workers may not be cognizant of specific signs and symptoms[2-3]. In addition, state health departments should request the CDC's assistance when necessary, and utilize the Laboratory Response Network for Bioterrorism, to collect and transport specimens for laboratory analysis[2-3]. If the results of an investigation point towards intentional release alert the CDC and federal/local/state law enforcement immediately.

Early on in a response, Anthrax Assist is available as a modeling tool created by CDC for use by local and state public health authorities. Anthrax Assist projects hospitalizations and casualties from a newly detected inhalation anthrax event in order to aid early postexposure prophylaxis initiation decision-making by providing scenario-specific information for developing quantitative response plans for this threat.[10]

Treatment guidelines as mentioned above should be considered, and if there are multiple casualties, then specific guidelines for clinical care and medical countermeasures for use during an anthrax mass-casualty incident should be followed.[11]

References

1. American Academy of Pediatrics. 2021 Red Book: Report of the Committee on Infectious Disease, 32nd Edition. Illinois, Academy of Pediatrics, 2021.
2. Bower W, Hoffmaster A, Shadomy S. Anthrax. In: Heymann DL, editor. Control of communicable diseases manual. 20th ed. Washington, DC: American Public Health Association; 2015. p. 16-26.
3. Anthrax [Internet]. Centers for Disease Control and Prevention; 2017 [cited 2017Apr12]. Available from: https://www.cdc.gov/anthrax/index.html
4. Anthrax [Internet]. Center for Infectious Disease Research and Policy, University of Minnesota; 2013 [cited 2017Apr12]. Available from: http://www.cidrap.umn.edu/infectious-disease-topics/anthrax
5. Arizona Department of Health Services. In: Case Definitions for Reportable Communicable Morbidities: 2021. 2021 [cited 2022Feb24]; Available from: https://www.azdhs.gov/documents/preparedness/epidemiology-disease-control/disease-investigation-resources/casedefinitions/case-definitions.pdf
6. Anthrax (*Bacillus anthracis)*– 2010 Case Definition [Internet]. National Notifiable Diseases Surveillance System (NNDSS). Centers for Disease Control and Prevention; [cited 2017Apr12]. Available from: https://wwwn.cdc.gov/nndss/conditions/anthrax/case-definition/2010/
7. Guide to Laboratory Services: Microbiology [Internet]. Arizona Department of Health Services. 2017Jan20 [cited 2017Apr12]. Available from: http://azdhs.gov/documents/preparedness/state-laboratory/public-health-microbiology/lab-guide.pdf
8. Arizona Administrative Code [Internet]. 2013Sep30 [cited 2017Apr12]. Available from: http://apps.azsos.gov/public_services/Title_09/9-06.pdf
9. Stern EJ, Uhde KB, Shadomy SV, Messonnier N. Conference Report on Public Health and Clinical Guidelines for Anthrax. Emerging Infectious Diseases [Internet]. 2008Apr [cited 2017Apr12];14(4). Available from: https://wwwnc.cdc.gov/eid/article/14/4/07-0969_article
10. Rainisch G, Meltzer MI, Shadomy S, Bower WA, Hupert N. Modeling Tool for Decision Support during Early Days of an Anthrax Event. Emerg Infect Dis. 2017;23(1):46-55.

doi:10.3201/eid2301.151787 Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5176207/

11. Bower WA, Hendricks K, Pillai S, Guarnizo J, Meaney-Delman D; Centers for Disease Control and Prevention (CDC). Clinical Framework and Medical Countermeasure Use During an Anthrax Mass-Casualty Incident. MMWR Recomm Rep. 2015 Dec 4;64(4):1-22. doi: 10.15585/mmwr.rr6404a1. Available from: https://www.cdc.gov/mmwr/pdf/rr/rr6404.pdf