BIOTERRORISM AGENTS

PUBLIC HEALTH SERVICES

JUNE 2003

Adapted from Santa Clara County Public Health Dept. – Zebra Packet

Stanislaus County HEALTH SERVICES AGENCY

DETECTING BIOTERRORISM - The Clinician's Role

Health care providers will be "first responders" in the event of a bioterrorism attack or other public health emergency. **Early detection by astute clinicians and rapid reporting to local public health will be critical** in minimizing the impact of a bioterrorism event or other disaster.

Bioterrorism attacks are likely to present as acute outbreaks of an unusual syndrome, or outbreak illnesses in the "wrong" season, or geographic area.

If you see patient(s) with any of the following clinical syndromes:

1. Acute severe pneumonia or respiratory distress
2. Encephalopathy
3. Acute onset neuromuscular symptoms
4. Otherwise unexplained rash with fever
5. Fever with mucous membrane bleeding
6. Unexplained acute icteric syndromes
7. Massive diarrhea with dehydration and collapse

In the setting of any of the following:

1. **Atypical host characteristics**:
   - Young (< 50 years)
   - Immunologically intact
   - No underlying illness
   - No recent international travel or other exposure to potential source of infection

2. **Serious, unexpected, acute illness**
   - Abrupt onset
   - Prostration
   - Cardiovascular collapse
   - Respiratory distress
   - Obtundation/change in mental status
   - Disseminated intravascular coagulation

3. **Multiple similarly presenting cases,** especially if
   - Geographically associated, or
   - Closely clustered in time

4. **Increases in common syndromes occurring out of season**
   - Influenza-like-illness in the summer

Please call HSA Public Health Services, Communicable Disease Control Unit <u>immediately.</u> We would like to hear from you even if you only have <u>some</u> suspicion that something isn't quite right.

During business hours (M-F, 8 am – 5 pm)	**209-558-5678**
After hours, call to speak with the on duty Communicable Disease staff person	**209-664-6032**

HEALTH SERVICES AGENCY

ANTHRAX

ALL SUSPECT CASES OF ANTHRAX MUST BE REPORTED IMMEDIATELY TO THE PUBLIC HEALTH SERVICES COMMUNICABLE DISEASE CONTROL UNIT:
During business hours: 209-558-5678
After hours : 209-664-6032

Epidemiology:

- Anthrax can be transmitted by inhalation, ingestion, or inoculation (inhalation is the most likely during a bioterrorist attack)
- The spore form of anthrax is highly resistant to physical and chemical agents; spores can persist in the environment for years
- **Anthrax is not transmitted from person to person**

Clinical:

- Incubation period is 1-5 days (range up to 43 days)
- Inhalation anthrax presents as acute hemorrhagic mediastinitis
- Biphasic illness, with initial phase characterized by nonspecific flu-like illness followed by acute phase characterized by acute respiratory distress and toxemia (sepsis)
- Chest x-ray findings: **Mediastinal widening in a previously healthy patient in the absence of trauma is pathognomonic for anthrax**
- Mortality rate for inhalation anthrax approaches 90%, even with treatment. Shock and death within 24 – 36 hours

Laboratory Diagnosis:

- Laboratory specimens should be handled in a Biosafety Level 2 facility (e.g. California state Microbial Diseases Laboratory)
- Gram stain shows gram positive bacilli, occurring singly or in short chains, often with squared off ends (safety pin appearance). In advanced disease, a gram stain of unspun blood may be positive
- Distinguishing characteristics on culture include: non-hemolytic, non-motile, capsulated bacteria that are susceptible to gamma phage lysis
- ELISA and PCR tests are available at national reference laboratories

Patient Isolation:

- Standard barrier isolation precautions. Patients do not require isolation rooms
- **Anthrax is not transmitted person to person**

Treatment:

- Prompt initiation of antibiotic therapy is essential
- Antibiotic susceptibility testing is KEY to guiding treatment
- Ciprofloxicin (400 mg IV q 12 hr) is the antibiotic of choice for penicillin-resistant anthrax or for empiric therapy while awaiting susceptibility results
- All patients should be treated with anthrax vaccine if available; antibiotic treatment should be continued until 3 doses of vaccine have been administered (day 0, 14 and 28). If vaccine is unavailable, antibiotic treatment should be continued for 60 days.

Prophylaxis:

- If vaccine is available, all exposed persons (as determined by local and state health depts) should be vaccinated with 3 doses of anthrax vaccine (days 0, 14 and 28)
- Start antibiotic prophylaxis immediately after exposure with ciprofloxicin (500 mg po q 12 hrs) or doxycycline (100 mg po q 12 hrs). (If strain is penicillin-susceptible, therapy can be modified to penicillin or amoxicillin.)
- Antibiotic prophylaxis should be continued until 3 doses of vaccine have been administered; if vaccine is unavailable, antibiotics should be continued for 60 days.

Medical Treatment and Response to Suspected Anthrax: Information for Health Care Providers During Biologic Emergencies March 2003

ALL SUSPECT CASES OF ANTHRAX MUST BE REPORTED IMMEDIATELY TO STANISLAUS COUNTY PUBLIC HEALTH SERVICES:

During Business Hours:

209-558-5678

After Hours (Nights, Weekends and Holidays):

209-664-6032

I. KEY SUMMARY POINTS

Epidemiology:

- Anthrax can be transmitted by inhalation, ingestion, or inoculation (inhalation is the most likely during a bioterrorist attack)
- The spore form of anthrax is highly resistant to physical and chemical agents; spores can persist in the environment for years
- **Anthrax is not transmitted from person to person**

Clinical:

- Incubation period is 1-5 days (range up to 43 days)
- Inhalation anthrax presents as acute hemorrhagic mediastinitis
- Biphasic illness, with initial phase characterized by nonspecific flu-like illness followed by acute phase characterized by acute respiratory distress and toxemia (sepsis)
- Chest x-ray findings: **Mediastinal widening in a previously healthy patient in the absence of trauma is pathognomonic for anthrax**
- Mortality rate for inhalation anthrax approaches 90%, even with treatment. Shock and death within 24 – 36 hours

Laboratory Diagnosis:

- Laboratory specimens should be handled in a Biosafety Level 2 facility (e.g. California state Microbial Diseases Laboratory)
- Gram stain shows gram positive bacilli, occurring singly or in short chains, often with squared off ends (safety pin appearance). In advanced disease, a gram stain of unspun blood may be positive
- Distinguishing characteristics on culture include: non-hemolytic, non-motile, capsulated bacteria that are susceptible to gamma phage lysis
- ELISA and PCR tests are available at national reference laboratories

Patient Isolation:

- Standard barrier isolation precautions. Patients do not require isolation rooms
- **Anthrax is not transmitted person to person**

Treatment:

- Prompt initiation of antibiotic therapy is essential
- Antibiotic susceptibility testing is KEY to guiding treatment
- Ciprofloxicin (400 mg IV q 12 hr) is the antibiotic of choice for penicillin-resistant anthrax or for empiric therapy while awaiting susceptibility results
- All patients should be treated with anthrax vaccine if available; antibiotic treatment should be continued until 3 doses of vaccine have been administered (day 0, 14 and 28). If vaccine is unavailable, antibiotic treatment should be continued for 60 days.

Prophylaxis:

- If vaccine is available, all exposed persons (as determined by local and state health depts) should be vaccinated with 3 doses of anthrax vaccine (days 0, 14 and 28)
- Start antibiotic prophylaxis immediately after exposure with ciprofloxicin (500 mg po q 12 hrs) or doxycycline (100 mg po q 12 hrs). (If strain is penicillin-susceptible, therapy can be modified to penicillin or amoxicillin.)
- Antibiotic prophylaxis should be continued until 3 doses of vaccine have been administered; if vaccine is unavailable, antibiotics should be continued for 60 days

ALL SUSPECT CASES OF ANTHRAX MUST BE REPORTED IMMEDIATELY TO STANISLAUS COUNTY PUBLIC HEALTH SERVICES

During Business Hours:

209-558-5678

After Hours (Nights, Weekends and Holidays):

209-664-6032

II. Introduction/Epidemiology

Anthrax is a disease caused by *Bacillus anthracis* which can infect most warm-blooded animals, including man. Transmission to humans usually occurs through contact with infected animals or contaminated animal products. Humans become infected by inoculation, inhalation, or ingestion of the bacterium. In humans, naturally-occurring anthrax primarily involves the skin or rarely, the lungs or the gastrointestinal tract. **The bacillus produces a resistant spore which could be dispersed as a small particle aerosol. In the event of a biologic terrorist attack, aerosolization is the most likely mode of transmission, and inhalational anthrax would be the predominant form of disease affecting persons exposed to the aerosol**.

The spore form of *B. anthracis* is highly resistant to physical and chemical agents. The organism has been shown to persist for years in factories contaminated during the processing of infected animal products. Soil, animal feed, and to a lesser extent, ground water are the major reservoirs for anthrax.

Although human anthrax is infrequent and sporadic in the United States and most other industrialized countries, human cases (primarily cutaneous) continue to be reported from Africa, Asia, Europe, and the Americas. Although anthrax-contaminated soil exists in many foci throughout the United States, the number of cases reported annually has declined throughout the last five decades; five human cases (all cutaneous anthrax) were reported between 1981-1996. **A suspected case of anthrax in a patient *without* a clear exposure history (e.g., a traveler returning from an area with known animal cases or a person with exposure to imported animal hides) may be the first clue of a bioterrorist attack. Therefore, even a single, suspect case should prompt immediate notification of STANISLAUS COUNTY PUBLIC HEALTH SERVICES (Business hours: 209-558-5678; After hours: 209-664-6032) Person to person transmission of anthrax is extremely rare.**

III. **Significance as a Potential Bioterrorist Agent**

- Anthrax has been weaponized by many countries during the last 50 years, including the United States (during the 1950's) and Iraq during the Gulf War.
- Anthrax is easy to cultivate and spores are readily produced.
- Anthrax spores are highly resistant to heat and disinfection.
- If aerosolized spores are inhaled, a severe hemorrhagic mediastinitis can occur with mortality rates approaching 90% even with appropriate treatment.
- Currently, anthrax vaccine is in limited supply in the United States and not available to the general public.

IV. **Clinical Manifestations**

During an act of bioterrorism, release of an aerosol will be the most likely route of transmission. Given this, most exposed individuals will present with symptoms of inhalation anthrax with only a few, if any, presenting with the cutaneous form of the disease. Gastrointestinal anthrax would be much less likely.

Inhalation Anthrax presents as acute hemorrhagic mediastinitis after inhalation of airborne particles contaminated with *B. anthracis* spores. Inhalation anthrax does **not** present as an acute pneumonia.

Incubation period - illness usually occurs within 1-5 days of exposure (may be as long as 43 days)
Symptoms - Typically biphasic illness

Initial Phase is characterized by flu-like symptoms:

mild, nonspecific respiratory illness
malaise, fatigue, myalgia
low-grade fever
nonproductive cough
mild chest discomfort (occasionally)
rhonchi may be heard, exam otherwise normal

Acute Phase develops after 2-5 days, it may be briefly preceded by 1-2 days of improvement. Characteristic findings include:
acute severe respiratory distress
dyspnea, cyanosis, stridor and profuse diaphoresis
subcutaneous edema of chest and neck
markedly elevated temperature, pulse, respiratory rate
moist crepitant rales

x-ray findings:
mediastinal widening in an otherwise healthy persons is a pathognomonic sign; pleural effusion may be present, evidence of pneumonia is often lacking

Shock develops rapidly, sometimes accompanied by evidence of hemorrhagic meningitis, and patients usually die within 24 hours of onset of the acute phase. In prior outbreaks, mortality rates approached 90% despite appropriate antibiotic therapy.

The differential diagnosis of acute mediastinitis includes: esophageal perforation; trauma; contiguous spread from a head, neck or thoracic infection; and postsurgical infections after cardiothoracic procedures. **Anthrax should be strongly considered in any previously healthy patient with acute mediastinitis.**

The diagnosis of inhalation anthrax requires a very high index of suspicion, most often based on epidemiologic evidence of a potential exposure. In the initial stages after a bioterrorist attack, a recognized source of exposure would likely be absent -- clinical suspicion is of utmost importance.

Cutaneous Anthrax: presents as a "malignant pustule or malignant carbuncle" resulting from introduction of the anthrax bacillus beneath the skin by inoculation or contamination of a pre-existent break in the skin.

Incubation period - ranges from 1-7 days but is commonly 2-5 days

Symptoms - an evolving skin lesion, usually located on the exposed parts of the

body (face, neck, arms), with a varying degree of associated edema. The skin lesion typically progresses as follows:

Small, painless, pruritic papule **>>>** small ring of vesicles that coalesce into a single large vesicle **>>>** vesicle ruptures to form depressed ulcer **>>>** 1-3 cm eschar develops in center (7-10 days from onset of lesion) **>>>** eschar falls off (after 1-2 weeks) leaving a permanent scar.

Systemic symptoms including fever, headache, myalgias, and regional lymphangitis/lymphadenopathy have been described. Lesions on the face and neck may be associated with significant edema and impingement of the trachea from neck swelling can occur. "Malignant edema" describes a syndrome with marked edema, induration and multiple bullae at the site of inoculation associated with generalized toxemia. Septicemia is rare. Untreated cutaneous anthrax has a case fatality rate up to 20%, but fatalities are rare (< 1%) with effective antibiotic treatment.

Gastrointestinal Anthrax: occurs after the ingestion of contaminated food, particularly raw or undercooked meat from infected animals.

Incubation period - ranges from 2-7 days

Symptoms - Two clinical presentations, *intestinal* and *oropharyngeal*, have been described. The symptoms of intestinal anthrax are initially nonspecific and include nausea, vomiting, anorexia and fever. As the disease progresses, abdominal pain, hematemesis and bloody diarrhea develop, occasionally accompanied by ascites. The patient may present with the findings of an acute surgical abdomen. Oropharyngeal anthrax is associated with cervical edema and necrosis. A lesion, resembling a cutaneous anthrax lesion, may be seen in the oral cavity on the posterior wall, the hard palate or the tonsils. Patients typically complain of fever, dysphagia and lymphadenopathy. Toxemia, shock and cyanosis characterize the terminal stages of both forms of the disease. The case fatality rate for gastrointestinal anthrax ranges from 25 to 60%.

Meningitis: Meningitis occurs in less than 5% of cases, and may be a complication of any form of anthrax (inhalational, gastrointestinal or cutaneous). Rarely does it occur without a primary focus. It is usually hemorrhagic.

Incubation period - concurrent with or one to several days after the onset of cutaneous, inhalation or gastrointestinal anthrax.

Symptoms - abrupt onset of meningeal symptoms including nausea, vomiting, myalgia, chills and dizziness. Laboratory findings are notable for a hemorrhagic meningitis. Encephalomyelitis and cortical hemorrhages have been reported; death occurs in 1-6 days.

V. Laboratory Diagnosis

Laboratory work with clinical specimens must be done under Biosafety Level 2 conditions. If infection with *Bacillus anthracis* is suspected, please *immediately* call STANISLAUS COUNTY PUBLIC HEALTH SERVICES at 209-558-5678 to arrange for submission of specimens to an appropriate reference laboratory for confirmatory testing. After hours call 209-664-6032 and request the "On Duty Communicable Disease (CD) Staff person."

- **Culture** is the definitive test for anthrax.

  Bacillus anthracis can be isolated from blood, pleural fluid, CSF, ascitic fluid, vesicular fluid or lesion exudate. Sputum cultures are rarely positive. When culturing a lesion, collect either vesicular fluid or exudate from the ulcer. If there is no visible exudate, lift the edge of the eschar with a pair of forceps and collect the fluid near the edge.

  Blood cultures may be positive for bacterial growth in 12-48 hours using standard technology; however, the ability of most clinical microbiology laboratories to definitively identify *B. anthracis* may be limited.

- **Microscopy**
  - **Gram stain**
    - Gram stain should be performed on vesicular fluid or exudate from ulcerative lesions for suspected cutaneous anthrax, pleural fluid for suspected inhalation anthrax, and CSF for suspected meningeal anthrax. **In advanced disease, a gram stain of unspun blood may be positive.** The Gram stain shows gram positive bacilli, usually occurring singly or in short chains, often

with squared-off ends (safety-pin appearance).

- **Direct Fluorescent Antibody (DFA) Test**
  - Rapid diagnostic staining technique. This test has been used to examine exudate from cutaneous lesions, CSF and tissue. Not generally helpful for inhalation anthrax because respiratory/pleural fluid specimens are usually negative in the early stages of disease when rapid diagnosis is most critical. This test is currently available only at national reference laboratories.
- **Rapid diagnostic tests**
  - An ELISA assay for protective antigen detection and PCR for detection of nucleic acid can provide a preliminary diagnosis of anthrax within several hours. Currently, these tests are only available at reference laboratories.

- ***Evaluation of a Blood Culture that is Suspicious for Anthrax:*** **The following steps are needed to presumptively identify anthrax in the microbiology laboratory:**

  - Overnight incubation on a blood or nutrient agar isolation plate
  - Gram stain shows large gram positive rods with square or concave ends
  - Blood agar colonies are non-hemolytic, rough, gray-white, tenacious colonies with comma- shaped protrusions
  - Subculture to blood agar plates to test for lysis with gamma phage and penicillin susceptibility. (**NOTE: Although naturally-occurring anthrax is penicillin-sensitive, in the event of a bioterrorist event, an anthrax strain resistant to penicillin may have been released.**)
  - Test for lack of growth on phenylethyl alcohol blood agar, lack of gelatin hydrolysis, and lack of salicin fermentation
  - The bacterial capsule can be demonstrated on nutrient agar containing 0.7% sodium bicarbonate incubated overnight in a candle jar. Examine for capsule with methylene blue or India ink.

To distinguish *Bacillus anthracis* from other *Bacillus species:* Distinguishing features include that *Bacillus anthracis* is non-hemolytic, non-motile, capsulated and susceptible to gamma phage lysis.

Summary: *Bacillus anthracis* is a gram positive bacillus that is white or gray in color, nonhemolytic or weakly so, nonmotile, gamma phage and usually penicillin susceptible, and able to produce the characteristic capsule.

- **Serology** - not helpful for rapidly establishing the diagnosis during the acute illness.

- **Autopsy Findings** - identifying thoracic hemorrhagic necrotizing lymphadenitis and hemorrhagic necrotizing mediastinitis in a previously healthy patient is essentially pathognomonic for inhalation anthrax. Hemorrhagic meningitis would also be a distinct clue to the diagnosis of anthrax.

****NOTE: In the event of a bioterrorist event, the anthrax strain may be penicillin resistant. There are currently no NCCLS standards for susceptibility testing for *B. anthracis*. Microbiology laboratories must alert STANISLAUS COUNTY PUBLIC HEALTH SERVICES Laboratory (209-558-5678, after hours 209-664-6032) as soon as *B. anthracis* is identified so that susceptibility testing at a national reference laboratory can be arranged. The results of susceptibility testing are crucial in guiding both therapy and prophylaxis for potentially infected persons.**

VI. Handling Laboratory Specimens

Biosafety Level 2 practices, containment equipment and facilities are recommended for procedures on clinical materials suspected as being positive for anthrax. Laboratory staff handling specimens from persons who might have anthrax must wear surgical gloves, protective gowns and shoe covers. Laboratory tests should be performed in Biological Safety Level 2 cabinets and blood cultures should be maintained in a closed system. Every effort should be made to avoid splashing or creating an aerosol, and protective eye wear and masks should be worn if work cannot be done in a Biological Safety Level 2 cabinet. A full-face mask respirator with a HEPA

(high efficiency particulate air) filter is an acceptable alternative to masks and protective eye wear, but use of this equipment is not mandatory.

Accidental spills of potentially contaminated material should be decontaminated immediately by covering liberally with a disinfectant solution (5% hypochlorite or 10% formalin), **left to soak for 30 minutes**, and wiped up with absorbent material soaked in disinfectant. All biohazardous waste should be decontaminated by autoclaving. Contaminated equipment or instruments may be decontaminated with a hypochlorite solution, hydrogen peroxide, iodine, peracetic acid, 1% glutaraldehyde solution, formaldehyde, ethylene oxide, copper irradiation or other O.S.H.A. approved solutions, or by autoclaving or boiling for 10 minutes.

VII. **Treatment**

The key to successful treatment is prompt administration of an antimicrobial at the first suspicion of anthrax. During a biologic emergency, before susceptibility is determined (which may take several days), assume penicillin and tetracycline resistance and treat with ciprofloxacin at 400 mg IV every 12 hours. Penicillin is the antibiotic of choice for treating infections with penicillin-sensitive anthrax.

Treatment for Non-Pregnant Adults:

Inhalation anthrax (this regimen also recommended for gastrointestinal and meningeal anthrax)

- For **penicillin resistant anthrax,** administer *ciprofloxacin* at 400 mg IV every 8 to 12 hours (Alternative quinolone options include: ofloxacin 400 mg IV every 12 hours or levofloxacin 500 mg IV every 24 hours). If the isolate is tetracycline susceptible, *doxycycline* 200 mg initially, followed by 100mg IV every 12 hours is equally efficacious.

- For **penicillin susceptible anthrax,** administer *Penicillin G* IV 80,000 units/kg body weight in the first hour followed by a maintenance dose of 320,000 units/kg body weight/day. The average adult dose is 4 million units every 4 hours; can also be administered as 2 million units every 2 hours. (*Amoxicillin* 500 mg IV every 8 hours is an alternative regimen, with a dosing schedule that may be easier to administer in the event of a large-scale outbreak.)

- Supportive therapy is often required (e.g., volume expanders, vasopressor

agents and oxygen). A tracheotomy may be needed if cervical edema compromises the airways.

Cutaneous anthrax

- *Mild disease*

  Penicillin susceptible anthrax - Potassium penicillin V orally at 30 mg/kg body weight/day in four equal portions every 6 hours, or amoxicillin 500 mg orally every 8 hours.

  Penicillin resistant anthrax - ciprofloxacin 500 mg orally every 12 hours or (if tetracycline susceptible) doxycycline 100 mg orally every 12 hours.

- *Extensive lesions*

  Penicillin susceptible anthrax - Penicillin G IV 2-4 million units every 4-6 hours or amoxicillin 500 mg IV every 8 hours.

  Penicillin resistant anthrax - Ciprofloxacin 400 mg IV every 12 hours or (if tetracycline susceptible) doxycycline 100 mg IV every 12 hours. When the edema and systemic symptoms have improved, treatment may be completed with the above oral regimens. In the absence of an aerosol exposure, therapy should be continued for 7-10 days. The skin lesions will continue to evolve despite the use of effective antibiotics but severe edema and systemic symptoms will be prevented. Glucosteroids for the first 3-4 days of treatment may reduce morbidity and mortality in severe cutaneous anthrax (malignant edema), particularly in the setting of laryngeal edema.

Alternative Therapies

******* In the event of severe penicillin allergy, documented resistance of *Bacillus anthracis* to penicillin, inability to administer the frequent IV dosing required for penicillin, or the exhaustion of penicillin supplies; **Ciprofloxacin (400 mg IV every 12 hours)**, **Ofloxacin (400 mg IV or orally every 8 to 12 hours)**, **Levofloxacin (500 mg IV or orally every 24 hours)** or **Doxycycline (100 mg IV every 12 hours)** (if proven susceptible) are the preferred alternatives.

In addition, the following drugs have been shown to have *in vitro* activity against anthrax and could potentially be used as alternative agents in the event of an

emergency, if the preferred antimicrobials listed above are unavailable or in short supply:

erythromycin	aminoglycosides	vancomycin
imipenem	cephalothin/cefazolin	chloramphenicol
clindamycin	tetracycline	extended-spectrum penicillins

***** In vitro testing suggests that *B. anthracis* is generally resistant to sulfamethoxazole, trimethoprim, cefuroxime, cefotaxime, ceftriaxone, ceftazadime, and aztreonam. Therefore, these antibiotics should not be used for treatment or prophylaxis of anthrax infection.*****

Treatment of Pediatric Patients and Pregnant Women:

- For **penicillin-resistant anthrax**, although ciprofloxacin is not generally given to children less than 16 years of age due to concerns about the development of arthropathy, the high mortality rate from anthrax infection weighs heavily in favor of using ciprofloxacin in this clinical situation. *Ciprofloxacin* should be given at 20-30 mg/kg/day orally or IV in 2 divided doses, not to exceed 1 gram/day.

- For **penicillin-susceptible anthrax**, *Penicillin G* is the drug of choice. The recommended intravenous dose **for children** with severe cutaneous anthrax, inhalation anthrax, or gastrointestinal anthrax is 250,000 units/kg body weight/day administered every 4 hours. *Amoxicillin* 500 mg IV every 8 hours for children > 20 kg and 40 mg/kg/day IV in divided doses every 8 hours for children < 20 kg, is an alternative antibiotic. Oral formulations can be used for milder disease or when IV therapy is not available.
- If ciprofloxacin supplies are exhausted and the patient is penicillin allergic or the anthrax strain is not susceptible to penicillin, *doxycycline* would be the preferred alternative agent (5 mg/kg/day IV or orally divided every 12 hours). Although doxycycline is not routinely administered to children < 8 years of age because of the risk of discoloration of teeth, the high mortality rate from systemic anthrax makes use of this agent the greater priority.
- *Penicillin G* is the drug of choice for **pregnant women,** if the isolate is

penicillin-susceptible. The dosing schedule is as outlined for adults above. *Ciprofloxacin*, although not routinely prescribed during pregnancy, is the preferred alternative drug for penicillin-resistant strains, as tetracyclines can result in rare but serious liver toxicity during pregnancy. If doxycycline is used because of exhaustion of quinolone supplies or severe allergy to either penicillin or ciprofloxacin, liver function tests should be performed.

Vaccination and Duration of Therapy

- All patients treated for inhalational anthrax should also receive anthrax vaccine due to the risk that delayed germination of mediastinal spores can result in disease recurrence. **Three doses of vaccine (Days 0, 14 and 28) should be administered.**

- In the absence of available anthrax vaccine, antibiotic treatment for inhalation anthrax should be continued for 60 days. (Patients should be switched to oral medications, as soon as possible.) If anthrax vaccine is available for postexposure vaccination, antibiotic therapy can be discontinued after three doses of vaccine (Days 0, 14, and 28) have been administered.

VIII. **Isolation of Patients**

Inhalation, cutaneous and gastrointestinal anthrax have never been transmitted directly from human-to-human. All staff should observe **Standard Precautions** when caring for patients with suspected or confirmed anthrax. In addition, the following is advised:

- For cutaneous anthrax, cover the lesion with a sterile dressing. Contact Wound and skin precautions should be observed for patients with skin lesions.
- Gloves should be worn for touching potentially infective material; gowns should be worn only if soiling is likely. Masks are not necessary, since patients with inhalation anthrax do not produce small particle aerosols containing sufficient spore counts (8,000 to 10,000 spores) to cause secondary infections.
- **HANDS MUST BE WASHED AFTER TOUCHING THE PATIENT OR POTENTIALLY CONTAMINATED ARTICLES AND BEFORE TAKING CARE OF ANOTHER PATIENT.**
- Patients do not require isolation rooms.

- Articles contaminated with infective material including bandages should be discarded and bagged and labeled before being sent for decontamination and reprocessing.

IX. Disposal of Infectious Waste

Use of tracking forms, containment, storage, packaging, treatment and disposal methods should be based upon the same rules as all other regulated medical wastes.

X. Autopsy and Handling of Corpses

All postmortem procedures should be performed using Universal Precautions.

- All persons performing or assisting in postmortem procedures must wear mandated P.P.E. (personal protective equipment) as delineated by O.S.H.A. guidelines.
- Instruments should be autoclaved or sterilized with a 10% bleach solution or other solutions approved by O.S.H.A. Surfaces contaminated during postmortem procedures should be decontaminated with an appropriate chemical germicide such as iodine, 10% hypochlorite or 5% phenol (carbolic acid).

XI. Management of Exposed Persons

In the event of a bioterrorist release of *Bacillus anthracis* spores, it may be difficult to define who has been exposed. Once the site of the attack is determined, all persons at the site of the release or downwind of the release (assuming an aerosol dispersal) would be considered potentially exposed.

Since inhalation anthrax does not spread from person to person, household and other contacts (such as healthcare workers caring for cases) of exposed persons are not considered exposed and do not require prophylaxis (unless they too were exposed to the aerosolized anthrax spores at the time of the attack).

- **Inhalational exposures:** Initiation of antibiotic therapy quickly after exposure has been shown to markedly reduce the mortality of inhalation anthrax in animal studies. The best available prophylactic regimen is the combination of antibiotic therapy and vaccination. Antibiotic susceptibility information on clinical isolates should guide prophylactic antibiotic choices.

While awaiting antibiotic susceptibility test results, or if susceptibility results confirm ***penicillin resistance***, begin therapy immediately with oral *ciprofloxacin* (500 mg po bid), *levofloxacin* (500 mg po per day), *ofloxacin* (400 mg po per bid), or *doxycycline* (100 mg po bid). If the isolate is ***penicillin susceptible***, *potassium penicillin V* (30 mg/kg/day in 4 divided doses) or *amoxicillin* (500 mg po every 8 hours) are the preferred preventive treatment.

- *Recommendations for prophylactic treatment of children, while awaiting antibiotic susceptibility results or if susceptibility results confirm* ***penicillin resistance****, include:* ciprofloxacin (20-30 mg per kg of body mass per day divided every 12 hours) or doxycycline (5 mg per kg of body mass per day divided every 12 hours). If the isolate is ***penicillin-susceptible***, all children should be treated with a penicillin antibiotic (for children weighing at least 20 kg, amoxicillin 500 mg po every 8 hours; for children < 20 kg, amoxicillin 40 mg per kg per day in divided doses every 8 hours).

- **Duration of antibiotic prophylaxis:** Therapy should be continued for at least 4 weeks, or until **three** doses of anthrax vaccine have been administered (Days 0, 14 and 28). **If vaccine is unavailable**, antibiotic prophylaxis should be continued for at least 60 days, and withdrawn under medical supervision.

- **Exposures through cuts, abrasions or injections:** Immediately wash the infected part, and apply a disinfectant solution such as hypochlorite solution. Promptly begin therapy as outlined under the treatment section for "Cutaneous anthrax-mild disease"; continue therapy for 7-10 days. Anthrax vaccine is not indicated.

- **Ingestional exposures:** Treat as for exposure by cuts or abrasions.

- **All persons exposed to anthrax should be instructed to watch for signs/symptoms of flu-like illness for at least 7 days.** Should such symptoms occur, patients must be immediately evaluated by a physician for the possible institution of intravenous antibiotic therapy.

- **VACCINATION** - An alum-absorbed, cell-free killed vaccine for anthrax has been developed and used primarily by the military and laboratory

workers/veterinarians. The vaccine efficacy against cutaneous anthrax has been documented for humans; evidence for protection against inhalation and gastrointestinal anthrax is limited to animal studies.

For prophylaxis, the vaccine is given parenterally (0.5mL subcutaneously) in three doses 2 weeks apart (Days 0, 14 and 28). Currently, there are limited vaccine supplies in the United States, and distribution is restricted to the military or persons at high-risk due to occupational exposures. (NOTE: Data from animal studies suggest that two doses of anthrax vaccine given two weeks apart may be sufficient, and in the setting of limited vaccine supplies may be a practical alternative).

Adverse reactions to anthrax vaccine are not common. About 6% of patients may develop a local reaction and 2-3% experience mild systemic symptoms. **(NOTE: The FDA has only licensed the vaccine for use in healthy adults aged 18-65 years; the safety and efficacy of the vaccine for children and pregnant women has not been studied).**

XII. **Reporting to the Health Department**

Human anthrax is a reportable disease in California. Although reporting of animal anthrax is not required by California regulations, we strongly urge reporting of **suspect animal cases as they may represent exposure to a bioterrorism attack.** ***All suspect human cases should be reported immediately by phone:***

- **During business hours**
  - Report suspect cases of *human and animal anthrax* to:
    STANISLAUS COUNTY PUBLIC HEALTH SERVICES at 209-558-5678
- **After business hours: 209-664-6032**

XIII. **References**

Benenson AS, ed. *Control of Communicable Diseases Manual*. 16th ed. Washington, DC: American Public Health Association; 1995:18-22.

Brachman PS. Anthrax. In: Hoeprich PD, Jordan MC, Ronald AR., eds. *Infectious Diseases: a treatise of infectious processes* . 5th ed. Philadelphia, PA: J.B. Lippincott Company; 1994:1003-1008.

Edward M. Anthrax. In: Feigin RD, Cherry JD, eds. *Textbook of Pediatric Infectious Diseases*. 3rd ed. Philadelphia, PA; 1992:1053-1056.

Fleming DO, Richardson JH, Tulis JJ, Vesley D, eds. *Laboratory Safety Principles and Practices* . 2nd ed. Washington, DC: American Society for Microbiology;1995:324.

Friedlander AM. Anthrax. In: Sidell FR, Takafuji ET, Franz DR, eds. *Textbook of Military*
Medicine. Washington, D.C.: Office of the Surgeon General at TMM Publications; 1997:467-478.

Inglesby TV, Henderson DA, Bartlett JG, et al. Anthrax: Civilian Medical and Public Health Management following use of a Biological Weapon. *JAMA* 1999: (in press).

LaForce FM. Anthrax. *Clin Infect Dis*. 1994;19:1009-1014.

Lew D. Bacillus Anthracis (Anthrax). In: Mandell G, Bennett J, Dolin R, eds. *Principles and Practice of Infectious Diseases* . 4th ed. New York: Churchill Livingstone; 1995:1885-
1889.

Meselson M, Guillemin J, Hugh-Jones M, et al. The Sverdlosk anthrax outbreak of 1979.
Science 1994;226:1202-1208.

Pile JC, Malone JD, Eitzen EM, Friedlander AM. Anthrax as a potential biological warfare agent. *Arch Intern Med*. 1998;158:429-434.

Turnbull PCB, Kramer JM. Bacillus. In: Balows A, Haulser WJ, Herrman KL, Shadomy HJ, eds. *Manual of Clinical Microbiology* 5th ed. Washington, DC: American Society for Microbiology; 1991:298-299.

US Army Medical Research Institute of Infectious Diseases. Medical Management of Biological Casualties. 3rd Edition. Fort Detrick, MD. 1998.

XIV. **Table 1: Inhalational Anthrax Treatment and Prophylaxis**

	Therapy	**Prophylaxis***
	Adult Doses	**Adult Doses**
Susceptibility Results Unknown or Penicillin-Resistant**	Ciprofloxacin 400mg IV q 8- 12h (*Alternative quinolones include:* ofloxacin 400mg IV q 8-12h or levofloxacin (500mg IV q 24h) Doxycycline 200mg IV x 1, then 100mg IV q 12h (*if tetracycline-susceptible*)	Ciprofloxacin 500mg po bid (*Alternative quinolones include:* ofloxacin 400mg po q 8- 12h or levofloxacin (500mg po q 24h Doxycycline 100mg po bid (*if tetracycline-susceptible*)
Penicillin-Susceptible	Penicillin G 80,000 units per kg in 1st hour followed by 320,000 units/kg/day. (*Average adult dose is 4 million units q 4hr or 2 million units q 2h*) Amoxicillin 500mg IV q 8h	Penicillin VK 30mg/kg/d in 4 divided doses Amoxicillin 500mg po q 8h

	Therapy	Prophylaxis*
	Pediatric Doses	**Pediatric Doses**
Susceptibility Results Unknown or Penicillin-Resistant	Ciprofloxacin 20-30mg/kg/day IV in 2 divided doses (*maximum daily dose not to exceed 1 gram/d*) Doxycycline (*if ciprofloxacin not available*) 4 mg/kg/d IV in 2 divided doses	Ciprofloxacin 20-30mg/kg per day po divided in 2 doses Doxycycline 5mg/kg/per day in 2 divided doses
Penicillin-Susceptible	Penicillin G 250,000 units/kg per day IV administered every 4 hours Amoxacillin 500mg IV q 8h if > 20kg or 40mg/kg per day IV divided into 3 doses if < 20kg	Penicillin VK 30 mg/kg per day po administered in 4 divided doses Amoxicillin 500mg po q 8h if > 20kg or 40mg/kg per day po divided in 3 doses if < 20kg

* Antibiotic prophylaxis should be continued for 60 days if anthrax vaccine is not available (*or if vaccine is available, antibiotics should be continued until 3rd dose of vaccine has been administered*).

** In pregnant women, penicillin-resistant anthrax should be treated with ciprofloxacin. If doxycycline is used, liver function tests should be monitored closely.

JUNE 2003 (Used with permission and adapted from Santa Clara County Health Department and Merced County Department of Public Health)

Stanislaus County HEALTH SERVICES AGENCY

BOTULISM

ALL SUSPECT CASES OF BOTULISM MUST BE REPORTED IMMEDIATELY TO THE PUBLIC HEALTH SERVICES COMMUNICABLE DISEASE CONTROL UNIT:

During business hours: 209-558-5678
After hours 209-664-6032

Epidemiology:

- Botulism neurotoxins (A-F) could be transmitted by aerosol or contamination of food and water supplies
- **Botulism is not transmitted from person to person**

Clinical:

- Incubation period is 12-36 hours (can be several days)
- Early symptoms include blurred vision, diplopia, and dry mouth
- Later symptoms include dysarthria, dysphagia, dysphonia, ptosis and the development of a symmetrical, descending progressive paralysis and respiratory failure
- Patients are usually alert and afebrile

Laboratory Diagnosis:

- Diagnosis is primarily based on a compatible clinical presentation
- Spinal protein is normal and characteristic findings are seen on EMG (facilitation of the compound muscle action potential on repetitive nerve stimulation)
- Toxin can be detected in serum (collect 30 cc in red top) and stool (foodborne botulism) by mouse neutralization bioassay performed at California Microbial Diseases Laboratory

Patient Isolation:

- Standard precautions. Patients do not require isolation rooms.

Treatment:

- Supportive care is the mainstay of therapy; prolonged ventilatory support is often required in severe cases
- Botulism anti-toxin (for A, B and E toxins) is in limited supply and is available only from the Division of Communicable Disease Control California Dept of Health Services

Prophylaxis:

- Currently, there is no available post-exposure prophylaxis

Medical Treatment and Response to Suspected Botulism: Information for Health Care Providers During Biologic Emergencies March 2003

ALL SUSPECT CASES OF BOTULISM MUST BE REPORTED IMMEDIATELY TO STANISLAUS COUNTY PUBLIC HEALTH SERVICES:

During Business Hours:

209-558-5678

After Hours (Nights, Weekends and Holidays):

209-664-6032

I. KEY SUMMARY POINTS

Epidemiology:

- Botulism neurotoxins (A-F) could be transmitted by aerosol or contamination of food and water supplies
- **Botulism is not transmitted from person to person**

Clinical:

- Incubation period is 12-36 hours (can be several days)
- Early symptoms include blurred vision, diplopia, and dry mouth
- Later symptoms include dysarthria, dysphagia, dysphonia, ptosis and the development of a symmetrical, descending progressive paralysis and respiratory failure
- Patients are usually alert and afebrile

Laboratory Diagnosis:

- Diagnosis is primarily based on a compatible clinical presentation
- Spinal protein is normal and characteristic findings are seen on EMG (facilitation of the compound muscle action potential on repetitive nerve stimulation)
- Toxin can be detected in serum (collect 30 cc in red top) and stool (foodborne botulism) by mouse neutralization bioassay performed at California Microbial Diseases Laboratory

Patient Isolation:

- Standard precautions. Patients do not require isolation rooms.

Treatment:

- Supportive care is the mainstay of therapy; prolonged ventilatory support is often required in severe cases
- Botulism anti-toxin is in limited supply and is available only from the Division of Communicable Disease Control, California Dept of Health Services

Prophylaxis:

- Currently, there is no available post-exposure prophylaxis

ALL SUSPECT CASES OF BOTULISM MUST BE REPORTED IMMEDIATELY TO STANISLAUS COUNTY PUBLIC HEALTH SERVICES

During Business Hours:

209-558-5678

After Hours (Nights, Weekends and Holidays):

209-664-6032

II. Introduction/Epidemiology

Botulism is a neuroparalytic disease caused by a neurotoxin produced by the anaerobic spore-forming bacterium, *Clostridium botulinum*. Two additional bacteria, *Clostridium barati* and *Clostridium butyricum,* can also occasionally produce botulinum toxin. Botulinum toxins are designated A through G based on antigenic differences. Human botulism is caused by toxin types A, B, E and rarely, F; botulism associated with toxin type A is most severe. In the eastern United States, botulism is primarily caused by the botulinum toxin type B. Botulism is classically acquired by the ingestion of preformed neurotoxin, although botulism can also be caused by localized infection with *C. botulinum* (wound botulism) or *C. botulinum* colonization of the intestine with in vivo toxin production (infant botulism).

Botulinum neurotoxins irreversibly bind to presynaptic receptors of peripheral nerves and subsequently inhibit release of acetylcholine. Both the neuromuscular junctions

and cholinergic autonomic synapses are affected, resulting in skeletal muscle and bulbar paralysis. Recovery can take weeks to months, requiring the regeneration of presynaptic axons and formation of new synapses.

Botulism in the United States is now most commonly recognized as wound botulism, which develops as a complication of injecting drug use. Botulism can also present in small clusters or single cases related to home-canned foods or vegetables of low acidity (*e.g., beans, peppers, carrots and corns)*. Recent examples of foodborne botulism due to non-preserved foods include foil-wrapped baked potatoes and sauteed onions. Foodborne botulism is always transmitted by foods that are not heated thoroughly before eating. In 1999, there were 26 cases of foodborne botulism and 41 cases of wound botulism reported in the U.S. Thirty eight of the 41 wound botulism cases were reported n California.

Airborne transmission of botulinum neurotoxin does not usually occur naturally, although three persons were infected by aerosolized toxin while disposing of rabbits and guinea pigs whose fur had been coated with previously aerosolized botulinum toxin during a laboratory accident in Germany in 1962. If used in a bioterrorist attack, aerosolization of preformed toxin would likely occur causing disease by the inhalation route. The clinical manifestations of disease would be identical to foodborne botulism, except for the absence of prodromal gastrointestinal symptoms. Deliberate contamination of food or water supplies is also possible.

Botulism is not transmitted by human-to-human contact.

An outbreak of botulism with the following characteristics should raise suspicion of a bioterrorist attack:

- An unusual toxin type for California
- Multiple, simultaneous cases with no common food exposure, no wounds, and no history of injecting drug use
- Absence of gastrointestinal prodromal symptoms would suggest an aerosolized route of exposure in patients with a clinical presentation compatible with botulism

III. **Significance as a Potential Bioterrorist Agent**

- Botulinum toxin is one of the most potent compounds known; it is 100,000 times more toxic than sarin.
- Could be released as an aerosol or used to contaminate water or food supplies.
- Iraq deployed 12,000 liters of botulinum toxin in over 100 munitions during the Gulf War in 1991.
- The Aum Shinrikyo cult released botulinum toxin during a failed bioterrorist attack in Japan.
- A massive outbreak of botulism would easily overwhelm both the existing supply of botulinum antitoxin and intensive care support (ventilator) capacity at acute care hospitals.

IV. **Clinical Manifestations**

During an act of bioterrorism, release of an aerosol will be the most likely route of transmission. The clinical presentation would be similar for both the inhalational and foodborne routes of transmission, with the exception that inhalational botulism would not have prominent gastrointestinal prodromal symptoms.

Incubation period - typically 12-36 hours, can be several days (dose-dependent). Inhalational botulism may have an incubation period up to 3 days.

Symptoms - Patients may exhibit some or all of the following signs or symptoms: These findings may appear in any order, the following represents the classical temporal relationship:

Early Symptoms (Cranial nerve abnormalities precede peripheral muscle weakness):

- blurred vision
- diplopia (double vision)
- dry mouth

Later Symptoms (more severe disease):

- dysphonia (hoarse voice)
- dysarthria (difficulty articulating words)
- dysphagia (difficulty swallowing)
- ptosis
- symmetrical, descending, progressive muscular weakness with fatiguability with repetitive muscle activity
- respiratory failure

The patient may have dilated or fixed pupils. Patients are typically alert and responsive and sensory deficits (other than blurred vision) do not occur. Deep tendon reflexes may be symmetrically depressed or remain normal. Fever does not occur unless there is a complicating infection.

The differential diagnosis of botulism includes myasthenia gravis and Lambert-Eaton myasthenic syndrome (lack autonomic features), tick paralysis (tick should be attached), acute inflammatory polyneuropathy (Guillain-Barre syndrome {GBS} usually begins with sensory complaints, rarely begins with cranial nerve abnormalities, and the progression of motor weakness may be ascending as opposed to the descending progression seen with botulism {except for the Miller-Fisher variant}; in addition, the CSF protein is usually elevated in GBS, although it may take 1 – 2 weeks to see an increase), polio (febrile illness with asymmetric weakness), magnesium intoxication and brain stem infarction.

The diagnosis of botulism requires a very high index of suspicion, and is most often based on epidemiologic evidence of a potential exposure. In the event of a bioterrorist attack, a recognized source of exposure may be absent. Clinical suspicion is of utmost importance.

V. Laboratory Diagnosis

A. Laboratory

Laboratory diagnosis is made by mouse neutralization assay, which is performed only at the California Microbial Disease Laboratory. If botulism is suspected, please call STANISLAUS COUNTY PUBLIC HEALTH SERVICES at 209-558-5678 to arrange for submission of specimens for testing. After hours call 209-664-6032 and request the "On Duty Communicable Disease (CD) Staff person."

The diagnosis of botulism requires a compatible clinical syndrome. The detection of botulinum neurotoxin in the patient's serum and/or stool (in the case of food-borne botulism) serves to confirm the diagnosis. The detection of toxin will be dependent on the total dose absorbed and the time from onset of symptoms to testing. The specimens will be evaluated by mouse neutralization bioassay, currently the gold standard assay. This assay can detect as little as 0.03 ng of botulinum toxin.

- Processing of Specimens
  - Obtain serum (draw 30 cc in a tube with no anticoagulant, refrigerate until well-clotted, centrifuge and separate the serum into a sterile tube for transport), stool (at least 25 gm), and gastric aspirate if available. Immediately call Stanislaus County Department of Public Health at 209-558-5678 (209-664-6032 after hours and request the "On Duty Communicable Disease (CD) Staff person.") to arrange for testing.
  - Serum specimens must be taken *before* antitoxin treatment to demonstrate the presence of botulinum toxin.
  - In California, anti-toxin and laboratory testing for toxin are available only from the state Department of Health Services. STANISLAUS COUNTY PUBLIC HEALTH SERVICES will facilitate routing of laboratory specimens and evaluation of need for anti-toxin.

- All specimens should be refrigerated, and not frozen, and examined as quickly as possible after collection. Freezing will hamper recovery of *Clostridium botulinum*, but will not prevent detection of toxin.

o Communication of Results

- Toxin test results may take up to 4 days to complete after specimens are received. Results will be given by Stanislaus County Department of Public Health. The lack of detection of toxin in serum of patients with clinically compatible illness does not necessarily rule out the diagnosis of botulism, particularly in the event of inhaled botulism neurotoxin.

o Bacterial cultures, antibody tests, and routine laboratory tests

- Blood, stool, sputum and urine cultures are not helpful in confirming a diagnosis of inhalational botulism.

- Patients do not generally develop an antibody response due to the subimmunogenic amount of toxin necessary to produce disease.

- Routine laboratory tests, including chemistries and hematologic profiles are generally within normal limits unless a secondary process (*e.g., nosocomial infection*) has occurred.

- Cerebrospinal fluid tests are generally normal in botulism (CSF protein may be elevated after 1 – 2 weeks with Guillain Barre Syndrome).

B. Electrophysiologic Studies - Should be performed on clinically-involved muscles

Tensilon test - normal (differentiates botulism from myasthenia gravis)

Nerve conduction velocity - normal

Repetitive nerve stimulation at 50 Hz - facilitation of the compound muscle action potential (rates 20-50 per second)(EMG shows an incremental response to repetitive stimulation)

These studies may support the diagnosis of botulism but a normal electromyelogram does not rule out disease.

VI. **Handling Laboratory Specimens**

Biosafety Level 2 practices, containment equipment and facilities are recommended for all activities with materials known or potentially containing toxin. Laboratory staff handling specimens from persons who might have botulism must wear surgical gloves, protective gowns, and shoe covers if performing procedures with high splash potential orrisk of aerosolization. Laboratory tests should be performed in Biological Safety Level 2 cabinets and blood cultures should be maintained in a closed system. Every effort should be made to avoid splashing or creating an aerosol, and protective eye wear and masks should be worn if work cannot be done in a Biological Safety Level 2 cabinet.

Accidental spills of potentially contaminated material should be decontaminated immediately by covering liberally with a disinfectant solution (a strong alkaline solution {e.g, 0.1M sodium hydroxide} for botulinum toxin or a 1:10 bleach solution for the *Clostridium* organism) for at least 15 minutes to ensure effective inactivation. If the material is suspected to contain both toxin and organisms, the spill must be sequentially treated with bleach and sodium hydroxide.

All biohazardous waste should be decontaminated by autoclaving. Contaminated equipment or instruments may be decontaminated with a hypochlorite solution, hydrogen peroxide, peracetic acid, 1% glutaraldehyde solution, formaldehyde, ethylene oxide, copper irradiation, or other O.S.H.A. approved solutions, or by autoclaving or boiling for 10 minutes.

VII. **Treatment**

Supportive care combined with the *rapid* administration of botulinal antitoxin are the keys to successful management of botulism. With improvements in intensive care support and early administration of antitoxin, mortality rates for botulism have been approximately 6% in recent years. Respiratory failure due to paralysis of respiratory muscles is the most serious complication as well as the most common cause of death.

- Botulinum Antitoxin - In uncontrolled studies, use of antitoxin has been associated with lower mortality rates and, if administered early after onset of symptoms, a shorter course of illness. A licensed trivalent antitoxin is available. Contrary to the package insert directions, current recommendations are to

administer ONE 10 ml vial of antitoxin per patient, intravenously in a normal saline solution over 20 minutes. Antitoxin need not be repeated since the circulating antibodies have a half-life of 5 to 8 days. Contact STANISLAUS COUNTY PUBLIC HEALTH SERVICES at 209-558-5678 (209-664-6032 after hours and request the “On Duty Communicable Disease (CD) Staff person.”) and they will assist in obtaining antitoxin from the state.

- The antitoxin is of equine origin and requires skin testing for hypersensitivity *before* administration of the antitoxin. About 9-21 % of patients will develop either acute or delayed-type sensitivity reactions. Serum sickness reactions appear to be dose-related and may be less likely with the newer dosing recommendations.

  Skin testing is performed by injecting 0.1 ml of a 1:10 dilution (in sterile physiologic saline) of antitoxin intradermally in the patient's forearm with a 26 or 27 gauge needle. The injection site should be monitored and the patient observed for allergic reactions for 20 minutes.

  The skin test is positive if any of the following occur:

  a. Hyperemic areola (> 0.5 cm) at the site of the injection

  b. Fever or chills

  c. Hypotension (greater than 20 mm Hg drop in blood pressure)

  d. Skin rash or generalized itching

  e. Respiratory difficulty

  f. Nausea or vomiting

- Supportive therapy - Improvements in intensive care have significantly decreased mortality rates for botulism. Monitoring of the vital capacity is crucial and intubation is usually indicated when the vital capacity falls below 12ml/kg, without waiting for a rise in PCO2 or fall in oxygen saturation. Ventilatory support may be required for weeks to months.

- Therapy in pediatric patients and pregnant women - therapy is identical to the recommendations outlined above.

- Aminoglycoside antibiotics are contraindicated for treatment of secondary

infections since they can exacerbate the neuromuscular blockade.

VIII. Isolation of Patients

Botulism has not been transmitted from human-to-human. All staff should observe Standard Precautions when caring for patients with suspected or confirmed botulism. Patients do not require isolation rooms.

IX. Disposal of Infectious Waste

Use of tracking forms, containment, storage, packaging, treatment and disposal methods should be based upon the same rules as all other regulated medical wastes.

X. Autopsy and Handling of Corpses

All postmortem procedures are to be performed using Universal Precautions.

- All persons performing or assisting in postmortem procedures must wear mandated P.P.E. (personal protective equipment) as delineated by O.S.H.A. guidelines.

- Instruments should be autoclaved or sterilized with a 10% bleach solution or other solutions approved by O.S.H.A. Surfaces contaminated during postmortem procedures should be decontaminated with an appropriate chemical germicide such as 10% hypochlorite or 5% phenol (carbolic acid).

XI. Management of Exposed Persons

An exposed person is defined as a person who has been directly exposed to botulinum neurotoxin. In the case of a bioterrorist event, the exposure will most likely occur by inhalation of toxin.

There is currently no available post-exposure prophylaxis for asymptomatic exposed persons. Such persons should be educated regarding the signs and symptoms of clinical botulism and instructed to seek medical care immediately if symptoms occur.

XII. Reporting to the Health Department

Botulism is a reportable disease in California. All suspect cases must be reported immediately to STANISLAUS COUNTY PUBLIC HEALTH SERVICES **by telephone:**

- **During business hours**
  - Call STANISLAUS COUNTY PUBLIC HEALTH SERVICES at 209-558-5678
- **After business hours**
  - Call 209-664-6032 and request the "On Duty Communicable Disease (CD) Staff person."

XIII. References

Allen SD, Baron EJ. Clostridium. In: Balows A, Haulser WJ, Herrman KL, Shadomy HJ, eds. *Manual of Clinical Microbiology* 5th ed. Washington, DC: American Society for Microbiology; 1991:505-521.

Arnon SS, Schechter R, Inglesby TV, et al. Botulinum toxin as a biological weapon: Medical and public health management. Consensus statement of the Working Group on Civilian Biodefense. *JAMA* 1999:

Bleck TP. Clostridium botulinum. In: Mandell G, Bennett J, Dolin R, eds. *Principles and Practice of Infectious Diseases*. 4th ed. New York: Churchill Livingstone;1995:2178-2182.

Centers for Disease Control and Prevention. Botulism in the United States, 1899-1996. Handbook for Epidemiologists, Clinicians, and Laboratory Workers, Atlanta, GA. Centers for Disease Control and Prevention, 1998.

Fleming DO, Richardson JH, Tulis JJ, Vesley D, eds. *Laboratory Safety Principles and Practices* . 2nd ed. Washington, DC: American Society for Microbiology;1995:324.
Holzer E. Botulism Caused by Inhalation. *Med. Klinik*. 1962;No. 41:1735-1740.

Shapiro RL, Hatheway C, Swerdlow DL. Botulism in the United States: A clinical and epidemiologic review. *Ann Intern Med* 1998;129:221-228.

Shapiro RL, Hatheway C, Becher J, Swerdlow DL. Botulism surveillance and emergency response: a public health strategy for a global challenge. *JAMA*. 1997;278:433-435.

JUNE 2003 (Used with permission and adapted from Santa Clara County Health Department and Merced County Department of Public Health)

Stanislaus County HEALTH SERVICES AGENCY

PLAGUE

ALL SUSPECT CASES OF PLAGUE MUST BE REPORTED IMMEDIATELY TO THE PUBLIC HEALTH SERVICES COMMUNICABLE DISEASE CONTROL UNIT:

During business hours: 209-558-5678
After hours : 209-664-6032

Epidemiology:

- Highly infectious after aerosolization
- Person-to-person and animal-to-human transmission can occur with pneumonic plague via respiratory droplet

Clinical:

- Incubation period is 1-3 days (ranges up to 7 days)
- Aerosolization would most likely result in pneumonic plague
- Pneumonic plague presents with acute onset of high fevers, chills, headache, malaise and a productive cough, that is initially watery before becoming bloody

Laboratory Diagnosis:

- Bacterial cultures (blood, sputum, or lymph node aspirate specimens) should be handled in a Biosafety Level 2 facility
- Wright, Giemsa, or Wayson stain shows gram negative coccobacilli with bipolar "safety-pin" appearance
- Organism grows slowly (48 hrs for observable growth) on standard blood and MacConkey agar
- Immunoflourescent staining for capsule (F1 antigen) is diagnostic

Patient Isolation:

- Strict respiratory isolation with droplet precautions (gown, gloves, and eye protection) until the patient has received at least 48 hours of antibiotic therapy and shows clinical improvement

Treatment:

- Streptomycin (1 g IM bid) or gentamicin (5 mg/kg IM or IV qd) are the preferred antibiotics
- Tetracyclines or flouroquinolones are alternative choices
- Co-trimoxazole is recommended for pregnant women and children between the ages of 2 months and 8 years
- Chloramphenicol should be used for plague meningitis

Prophylaxis:

- Antibiotic prophylaxis is recommended for all persons exposed to the aerosol or persons in close physical contact with a confirmed case
- Tetracyclines or flouroquinolones are recommended for 7 days from last exposure to a case

Medical Treatment and Response to Suspected Plague: Information for Health Care Providers During Biologic Emergencies March 2003

ALL SUSPECT CASES OF PLAGUE MUST BE REPORTED IMMEDIATELY TO

STANISLAUS COUNTY PUBLIC HEALTH SERVICES:

During Business Hours:

209-558-5678

After Hours (Nights, Weekends and Holidays):

209-664-6032

I. KEY SUMMARY POINTS

Epidemiology:

- Highly infectious after aerosolization
- Person-to-person and animal-to-human transmission can occur with pneumonic plague via respiratory droplet

Clinical:

- Incubation period is 1-3 days (ranges up to 7 days)
- Aerosolization would most likely result in pneumonic plague
- Pneumonic plague presents with acute onset of high fevers, chills, headache, malaise and a productive cough, that is initially watery before becoming bloody

Laboratory Diagnosis:

- Bacterial cultures (blood, sputum, or lymph node aspirate specimens) should be handled in a Biosafety Level 2 facility
- Organism grows slowly (48 hrs for observable growth) on standard blood and MacConkey agar
- Immunoflourescent staining for capsule (F1 antigen) is diagnostic

Patient Isolation:

- Strict respiratory isolation with droplet precautions (gown, gloves, and eye protection) until the patient has received at least 48 hours of antibiotic therapy and shows clinical improvement

Treatment:

- Streptomycin (1 g IM bid) or gentamicin (5 mg/kg IM or IV qd) are the preferred antibiotics
- Tetracyclines or flouroquinolones are alternative choices

- Co-trimoxazole is recommended for pregnant women and children between the ages of 2 months and 8 years

- Chloramphenicol should be used for plague meningitis

Prophylaxis:

- Antibiotic prophylaxis is recommended for all persons exposed to the aerosol or persons in close physical contact with a confirmed case

- Tetracyclines or flouroquinolones are recommended for 7 days from last exposure to a case

---

ALL SUSPECT CASES OF SMALLPOX MUST BE REPORTED IMMEDIATELY TO STANISLAUS COUNTY PUBLIC HEALTH SERVICES

During Business Hours:

209-558-5678

After Hours (Nights, Weekends and Holidays):

209-664-6032

II. Introduction/Epidemiology

Plague is transmitted by a gram-negative bacillus, Yersinia pestis, of the family Enterobacteriaceae. Plague is a zoonosis and can be transmitted by flea vectors from rodents to humans, and by respiratory droplets from animals to humans and humans to humans. Plague has three clinical forms: bubonic, primary septicemic and pneumonic disease. **Primary pneumonic plague would be the most likely presentation in the event of a biological attack.**

Naturally-occurring plague is a disease primarily affecting rodents. Transmission between rodents is via infected fleas. Transmission to humans can occur by respiratory droplets from rodents, from other infected animals/materials to humans or from human to human. In the United States, transmission to humans has been primarily from the bites of fleas from infected rodents. Less frequently, infection is caused by direct contact with body fluids or tissues while handling an infected animal. Currently in the

United States, infected cats are the only source of primary pneumonic plague for humans, since persons who develop secondary plague pneumonia usually receive appropriate isolation and treatment before secondary transmission can occur.

Human plague has been reported most often from the four western states of New Mexico, Arizona, Colorado and California. In the United States, 341 cases of human plague were reported during 1970-1995; the overwhelming majority of cases were bubonic plague.

Since primary pneumonic plague can be transmitted from person to person, patients with compatible clinical symptoms should be placed in respiratory isolation.

III. Significance as a Potential Bioterrorist Agent

- Could be released as an aerosol during a bioterrorist attack
- Has been weaponized by both the United States, former Soviet Union and Japan. Japan purportedly released plague over China during World War II.
- Potential for secondary transmission is highest with pneumonic plague.
- Aerosolized plague would cause pneumonic disease, with high mortality rates if untreated.

IV. Clinical Manifestations

During an act of bioterrorism, release of an aerosol will be the most likely method of dispersal, so that most patients will present with primary pneumonic plague.

A. Primary Pneumonic Plague

Incubation period - typically 1-3 days (ranges up to 7 days)

Symptoms - Patients exhibit acute and often fulminant onset of high fever, malaise, headache, myalgias and cough with production of sputum that is initially watery, before becoming bloody. Pneumonia rapidly progresses to dyspnea, stridor and cyanosis. Patients may develop respiratory failure, shock and ecchymoses.

B. Primary Septicemic Plague

Incubation period - 1-7 days

Symptoms - Clinically resembles septicemia caused by other gram negative bacteria. Patients are febrile and often have chills, headache, malaise and gastrointestinal disturbances. May progress rapidly to septic shock, consumptive coagulopathy, meningitis and coma. Patients may develop secondary plague pneumonia.

C. Bubonic Plague

Incubation period - 2-7 days

Symptoms - Patients develop fever, headache, chills and swollen, extremely painful lymph nodes (buboes). Nausea, vomiting and diarrhea are common. Swollen nodes typically involve the nodes that drain the site of initial infection. Patients generally do not have overlying skin lesions. Patients may develop secondary septicemic plague or secondary plague pneumonia.

V. Laboratory Diagnosis

Laboratory work must be done in Biosafety Level 2 facilities. If plague is suspected, please *immediately* call STANISLAUS COUNTY PUBLIC HEALTH SERVICES at 209-558-5678 to arrange for submission of specimens to an appropriate reference laboratory for confirmatory testing. After hours call 209-664-6032 and request the "On Duty Communicable Disease (CD) Staff person."

The diagnosis of plague may be suspected based on characteristic findings on microscopic staining of appropriate body fluids and confirmed by immunofluorescent staining for the capsule or bacterial culture. Serology is generally used retrospectively to confirm suspect cases.

- **Staining of Specimens**
  - Appropriate clinical specimens include: blood, bubo aspirates, sputum, CSF (if signs/symptoms of meningitis) and skin scrapings (if a lesion is present).

- **Gram stain**: polymorphonuclear leukocytes and bipolar staining, "safetypin" ovoid, gram-negative cocco-bacilli identified in bubo aspirate, sputum or CSF are highly suggestive of plague.

- **Wayson stain**: *Yersinia pestis* appears as light blue bacilli with dark blue polar bodies on a contrasting pink ground.

- **Immunofluorescent staining of capsule (F1)**: A positive finding is diagnostic. Must use fresh specimens to avoid false negatives. This test is available only at reference laboratories.

o **Bacterial cultures**

Blood, bubo aspirates, sputum, CSF and skin scrapings can be cultured.

Materials should be inoculated into blood and MacConkey agar plates and infusion broth. It generally takes 2 days to identify visible colonies. Rapid biochemical identification systems may not be reliable for identification due to slower growth rate of *Y. pestis.*

o **Serologic Testing**

Several serologic tests are available including a passive hemagglutination test (CDC). A fourfold or greater rise is diagnostic, a single titre of > 1:16 in someone without prior immunization against plague is suggestive. Serology is not useful for rapid diagnosis.

VI. Handling Laboratory Specimens

Laboratory staff handling specimens from persons who are suspected of having plague should follow Biosafety Level 2 precautions. Staff must wear surgical gloves, protective gowns and shoe covers. Laboratory tests should be performed in Biological Safety Level 2 cabinets, and blood cultures should be maintained in a closed system. Every effort should be made to avoid splashing or creating an aerosol, and protective eye wear and masks should be worn if work cannot be done in a Biological Safety Level 2 cabinet.

Laboratories working with a large amount of organism or doing studies on antibiotic resistant strains should use Biological Safety Level 3 cabinets. A full-face mask respirator with a HEPA (high efficiency particulate air) filter is an acceptable but

cumbersome alternative to masks and protective eye wear.

Accidental spills of potentially contaminated material should be decontaminated immediately by covering liberally with a disinfectant solution (0.1% sodium hypochlorite or sodium hydroxide (0.1N)). All biohazardous waste should be decontaminated by autoclaving. Contaminated equipment or instruments may be decontaminated with a hypochlorite solution, hydrogen peroxide, peracetic acid, 1% glutaraldehyde solution, formaldehyde, ethylene oxide, copper irradiation, or other O.S.H.A. approved solutions, or by autoclaving or boiling for 10 minutes.

VII. **Treatment**

Supportive care combined with the rapid administration of parenteral antibiotics are the keys to successful management of plague. Plague pneumonia is almost always fatal if antibiotics are not begun within 24 hours of onset of symptoms.

- **Recommended Antibiotics**
  The drug of choice for primary pneumonic plague is **streptomycin** [30 mg /kg/day administered by intramuscular injection every 12 hours (15 mg/kg) for 10 days]. However, since streptomycin may be in short supply, **Gentamicin** [1.7 mg/kg every 8 hours intravenously or intramuscularly for 10 days] and **doxycycline** [200mg intravenous loading dose, followed by 100mg IV every 12 hours for 10-14 days] are alternative agents.

  Chloramphenicol should be used for plague meningitis due to its better CNS penetration [loading dose of 25 mg/kg intravenously followed by 50-75 mg/kg/day divided into four equal doses; continue for 10 days after clinical improvement].

  Antibiotic choice may need to be altered as susceptibility information becomes available.

- **Alternative Antibiotics**
  Ciprofloxacin [400 mg intravenously every 12 hours], **Levofloxacin** [500 mg intravenously every 24 hours], and **Ofloxacin** [400 mg orally every 12 hours] are acceptable alternative agents. The efficacy of quinolones in humans has not been formally evaluated.

Bactrim [1 double-strength tablet orally every 12 hours or its intravenous equivalent] may also be efficacious based on animal and in vitro studies. Much less effective drugs (**do not use** unless all other alternatives are unavailable) include: rifampin, aztreonam, ampicillin, ceftazadime, cefotetan and cefazolin.

- **Supportive therapy** - Supportive care is essential, including intravenous fluids and hemodynamic monitoring.

- **Therapy in pediatric patients**
  First-line agents: **streptomycin** [15 mg/kg intramuscularly every 12 hours] or **gentamicin** [1.7 mg/kg intramuscularly or intravenously every 8 hours].

  Alternatively:

  If > or = 8 years of age - **Doxycycline**
  [100 mg intravenously or orally every 12 hours if > 45 kg;
  2.2mg/kg intravenously or orally every 12 hours if < 45 kg],

  If < 8 years of age - **Co-trimoxazole**
  [4 mg/kg orally or intravenously every 12 hours].

  Newborns up to age 2 months -**Ciprofloxacin**
  [10-20 mg/kg intravenously or orally twice daily
  Do not exceed 1 gram/day.

- **Therapy in pregnant women** - Avoid streptomycin in pregnancy due to its association with irreversible deafness in children exposed in utero. Gentamicin can be used (1.7 mg/kg every 8 hours). **Bactrim DS [1 tablet twice daily or its I.V. equivalent] is the preferred therapy for pregnant women, except at term, when a fluoroquinolone** (Ciprofloxacin 500 orally or intravenously every 12 hours) **is preferred**. If worsening illness, add a tetracycline agent as the benefits outweigh the risks. (NOTE: Liver function tests should be monitored due to potential hepatotoxicity with tetracycline use during pregnancy.)

VIII. Isolation of Patients

Pneumonic plague can be spread from person-to-person by droplet transmission (coughing, sneezing). All staff should observe **Standard Precautions** when caring for patients with suspected or confirmed plague. Patients with **pneumonic plague** should be placed on **strict respiratory isolation with Droplet Precautions until 48 hours of appropriate antibiotics** have been administered AND the patient is showing clinical

improvement. Droplet precautions require that the patient be placed in a private room and that persons entering the patient room wear a surgical mask, especially when within three feet of the patient. *Negative pressure rooms are not indicated*. Transmission can occur from plague skin lesions (such as draining buboes or abscesses) to contacts; wound and skin precautions should be followed if skin lesions are present. Multiple patients with pneumonic plague may be cohorted as long as all patients are receiving appropriate therapy.

IX. Disposal of Infectious Waste

Use of tracking forms, containment, storage, packaging, treatment and disposal methods should be based upon the same rules as all other regulated medical wastes.

X. Autopsy and Handling of Corpses

All postmortem procedures are to be performed using Universal Precautions. Efforts should be made to avoid aerosolization.

- All persons performing or assisting in postmortem procedures must wear mandated P.P.E. (personal protective equipment) as delineated by O.S.H.A. guidelines.
- Instruments should be autoclaved or sterilized with a 10% bleach solution or other solutions approved by O.S.H.A. Surfaces contaminated during postmortem procedures should be decontaminated with an appropriate chemical germicide such as 10% hypochlorite or 5% phenol (carbolic acid).

XI. Management of Exposed Persons

An exposed person is defined as a person who has been exposed to aerosolized *Yersinia pestis* or has been in close physical contact with a confirmed case-patient (contact at less than 2 meters during a period when the case was symptomatic and before the case had received 48 hours of antibiotic therapy). Household contacts and healthcare worker contacts should be considered exposed and should receive prophylaxis.

Antibiotics: **All antibiotic therapy should continue for 7 days from *last exposure* to the case. Decisions on antibiotic therapy should be based on susceptibility results.**

Non-pregnant Adult Post-Exposure Prophylaxis

Tetracycline 500 mg every 6 hours, orally

Doxycycline 100 mg every 12 hours, orally

Ciprofloxacin 500 mg every 12 hours, orally

Ofloxacin 400 mg every 12 hours, orally

Levofloxacin 500 mg every 24 hours, orally

Alternative Therapy

Trimethoprim / sulfamethoxazole 40 mg/kg/day in 2 equal doses at 12 hour intervals, orally.

Pediatric Post-Exposure Prophylaxis - Co-trimoxazole is the preferred antibiotic, or when benefits outweigh the risks, consider use of doxycycline or fluoroquinolones.

If > or = 8 years of age:
Doxycycline: If > or = 45 kg - 100 mg orally every 12 hours
If < 45 kg - 2.2 mg/kg orally every 12 hours

If < 8 years of age:
Co-trimoxazole: 4 mg/kg orally every 12 hours
Chloramphenicol: 25 mg/kg orally every 12 hours

Newborns up to age 2 months:
Ciprofloxacin: 10-20 mg/kg orally twice daily, do not exceed 1 gram/day.

Pregnant Women Post-Exposure Prophylaxis - Co-trimoxazole [1 DS tablet orally twice daily], is the preferred antibiotic, except at term, when the risk of kernicteris is greatest -- use fluoroquinolones [ciprofloxacin 500 mg orally twice daily]

XII. **Reporting to the Health Department**

Plague is a reportable disease in California. All suspect cases must be reported immediately to STANISLAUS COUNTY PUBLIC HEALTH SERVICES **by telephone:**

- **During business hours**
  - Call STANISLAUS COUNTY PUBLIC HEALTH SERVICES at 209-558-5678
- **After business hours**
  - Call 209-664-6032 and request the "On Duty Communicable Disease (CD) Staff person."

XIII. **References**

Benensen AS, ed. *Control of Communicable Diseases Manual*. 16th ed. Washington, DC: American Public Health Association; 1995:353-358.

Fleming DO, Richardson JH, Tulis JJ, Vesley D, eds. *Laboratory Safety Principles and Practices* . 2nd ed. Washington, DC: American Society for Microbiology;1995:324. Centers for Disease Control. Prevention of plague. MMWR. 1996;45 (Supplement RR-14):1-15.

Henderson DA, Inglesby TV, Bartlett JG, et al. Plague: Civilian Medical and Public Health Management following use of a Biological Weapon. *JAMA* 1999:

Inglesby TV, Henderson DA, Bartlett JG, et al. Plague: Medical and Public Health Management following use of a biological weapon. Consensus statement of the working group on civilian biodefense. *JAMA* 1999: (in press)

Perry RD, Fetherston JD. Yersinia pestis- Etiologic agent of plague. Clin Micro Reviews. 1997;10:35-66.

US Army Medical Research Institute of Infectious Diseases. Medical Management of Biological Casualties. 3rd Edition. Fort Detrick, MD. 1998.

JUNE 2003 (Used with permission and adapted from Santa Clara County Health Department and Merced County Department of Public Health)

Q FEVER

ALL SUSPECT CASES OF Q FEVER MUST BE REPORTED IMMEDIATELY TO THE PUBLIC HEALTH SERVICES COMMUNICABLE DISEASE CONTROL UNIT:

During business hours: 209-558-5678
After hours: 209-664-6032

Epidemiology:

- *Coxiella burnettii* is highly infectious by the aerosol route
- Q Fever is **rarely** transmitted from person to person

Clinical:

- Incubation period is 10-40 days
- Acute infection may be asymptomatic or a self-limited febrile illness
- Chest x-ray evidence of pneumonia is present in up to 50% of cases
- Mortality rate is less than 2%

Laboratory Diagnosis:

- Requires serologic confirmation (IFA or ELISA)
- Isolation of organism is not recommended due to significant hazards from handling bacterial cultures in the laboratory

Patient Isolation:

- Universal precautions. Respiratory isolation not required.

Treatment:

- Illness usually resolves **without** treatment
- Tetracyclines are the antibiotics of choice for more severe illnesses

Prophylaxis:

- Tetracycline antibiotics are very effective if administered **8 to 12 days AFTER exposure**
- Starting prophylaxis immediately after exposure can delay symptom onset but does not prevent illness

Medical Treatment and Response to Suspected Q Fever: Information for Health Care Providers During Biologic Emergencies March 2003

ALL SUSPECT CASES OF Q FEVER MUST BE REPORTED IMMEDIATELY TO STANISLAUS COUNTY PUBLIC HEALTH SERVICES:

During Business Hours:

209-558-5678

After Hours (Nights, Weekends and Holidays):

209-664-6032

I. KEY SUMMARY POINTS

Epidemiology:

- *Coxiella burnettii* is highly infectious by the aerosol route
- Q Fever is **rarely** transmitted from person to person

Clinical:

- Incubation period is 10-40 days
- Patients are usually alert and afebrile
- Acute infection may be asymptomatic or a self-limited febrile illness
- Chest x-ray evidence of pneumonia is present in up to 50% of cases
- Mortality rate is less than 2%

Laboratory Diagnosis:

- Requires serologic confirmation (IFA or ELISA)
- Isolation of organism is not recommended due to significant hazards from handling bacterial cultures in the laboratory

Patient Isolation:

- Universal precautions. Patients do not require isolation rooms.

Treatment:

- Illness usually resolves **without** treatment
- Tetracyclines are the antibiotics of choice for more severe illnesses

Prophylaxis:

- Tetracycline antibiotics are very effective if administered **8 to 12 days AFTER exposure**
- Starting prophylaxis immediately after exposure can delay symptom onset but does not prevent illness

ALL SUSPECT CASES OF Q FEVER MUST BE REPORTED IMMEDIATELY TO STANISLAUS COUNTY PUBLIC HEALTH SERVICES

During Business Hours:

209-558-5678

After Hours (Nights, Weekends and Holidays):

209-664-6032

II. Introduction/Epidemiology

Q fever is a zoonotic disease caused by *Coxiella burnetii,* a rickettsia-like organism. *C. burnetii* is unable to replicate outside host cells, but there is a spore-like form of the organism that is extremely resistant to heat, dessication and many standard antiseptic compounds. The organism can persist in the environment for long periods under harsh conditions. Despite the inherent resilience of *C. burnetii* and its ease in transmissibility, generally by inhaled aerosols, the acute clinical disease of Q fever is usually benign, although temporarily incapacitating.

Coxiella burnetii is extremely infectious. Humans have been infected most commonly by contact with domestic livestock, particularly goats, cattle and sheep but household pets, notably cats, have also been associated with infection. The risk is highest when humans are exposed to these animals at parturition, presumably via aerosolization of the organism from the uterus during birthing. *Coxiella* organisms can persist in the local environment, and produce infection, for weeks or months after contamination.

Q fever has VERY RARELY been transmitted from person-to-person (specifically, transmission has occurred to attendants during autopsies and from an infected patient to the attending obstetrician during delivery). **Persons exposed to an aerosol of *Coxiella burnetii* do not present a risk for secondary transmission to others or for reaerosolization of the organism.**

III. **Significance as a Potential Bioterrorist Agent**

- The spore-like form of the organism is resistant to heat and dessication, and can persist in the environment for long periods of time.
- Highly infectious when aerosolized and inhaled; a single organism may cause clinical illness
- Aerosolized *Coxiella burnetii* can result in an incapacitating respiratory illness; however, severe illness and fatalities are rare.

IV. **Clinical Manifestations**

During an act of bioterrorism, release of an aerosol will be the most likely route of transmission.

A. Acute Q Fever

Incubation period - 10 - 40 days, duration of the incubation period is inversely correlated with the size of the inoculum.

Symptoms - Acute disease is **not** clinically distinct, and illness resembles viral respiratory infections or atypical pneumonias. Can be divided into 3 main categories: (1) asymptomatic infection (seroconversion) - occurs in up to 50% of exposed persons, (2) self-limited febrile flu-like illness without pneumonia lasting 2 to 14 days and (3) pneumonia. Hepatitis, meningo-encephalitis, myocarditis, and pericarditis may be present acutely but are relatively uncommon.

Symptomatic patients exhibit any combination of the following (in order of decreasing frequency of appearance):

SYMPTOM	RELATIVE FREQUENCY (%)
fever (present in all symptomatic patients)	80-100
chills, rigors	75-100
severe headache, **retroorbital pain (may be a useful clue to diagnosis)**	50-100
fatigue, anorexia, weight loss	50-85
cough	50-60

myalgia	45-84
pleuritic chest pain	40-50
nausea, vomiting	15-20
diarrhea	5-20
neck stiffness	5-7

Pneumonia -Chest x-ray evidence of pneumonia may be present in up to 50% of patients. There are three possible presentations: (a) atypical pneumonia (dry nonproductive cough) (b) rapidly progressive pneumonia (often mimicking Legionnaire's disease), or (c) pneumonia with fever but no pulmonary symptoms [most common clinical scenario for acute Q fever]. *Radiographic findings*: Variable; may have pleural-based opacities, multiple rounded opacities, about 35% have pleural effusion, hilar adenopathy is uncommon.

Duration - 2 days - 2 weeks

Mortality - Low, estimated to be about 2% (usually in patients with co-morbid conditions)

B. Chronic Q Fever

Chronic infection due to Q fever is uncommon, occurring in less than 1% of acute infections. Endocarditis is the usual manifestation of Q fever but a wide array of syndromes have been described including: infection of vascular grafts, osteomyelitis, infectious arthritis, chronic hepatitis, pseudotumor of the lung, chronic pulmonary fibrosis, infection during pregnancy with miscarriage and prolonged fever.

Incubation period - varies, can be months to several years

Symptoms - Variable depending on specific clinical syndrome. Most often diagnosed in patients with either a cardiovascular abnormality (valvulopathy, prosthesis or aneurysm) or an underlying immunocompromised state (i.e., HIV infection or cancer).

V. Laboratory Diagnosis

ALL SUSPECT CASES OF Q FEVER MUST BE REPORTED IMMEDIATELY TO STANISLAUS COUNTY PUBLIC HEALTH SERVICES:

During Business Hours:

209-558-5678

After Hours (Nights, Weekends and Holidays):

209-664-6032

The diagnosis of Q Fever requires a high index of suspicion since the disease often presents with nonspecific symptoms which can be difficult to distinguish from viral illnesses or atypical pneumonia. The diagnosis is generally confirmed serologically; most laboratories are not equipped to isolate *Coxiella burnetii* and isolation of the organism is not recommended due to the significant hazards from handling bacterial cultures in the laboratory.

- **Serology**
  Several assays are available; antibody detection by indirect fluorescent antibody (IFA) or ELISA are used most commonly and appear to be the most sensitive. Significant IgM antibody does not appear until 2-3 weeks into illness and may persist for years. Acute and convalescent (2-3 months after onset of illness) antibody titres show a four-fold rise. In acute Q fever, antibodies to phase II antigens are higher than those to phase I antigens, in chronic Q fever the reverse occurs. Antibodies of the IgM type are usually observed for the first 6-12 months after infection, with IgG persisting afterward.

VI. Handling Laboratory Specimens

Laboratory staff handling specimens from persons who might have Q fever must wear surgical gloves, protective gowns, and shoe covers. Laboratory tests, such as serological examinations and staining of tissue impression smears, can be performed in Biological Safety Level 2 cabinets; although not recommended, blood cultures should be maintained in a closed system. Every effort should be made to avoid splashing or creating an aerosol. Biosafety Level 3 practices and facilities should be

used for inoculation, incubation and harvesting of cell cultures and the manipulation of infected tissues.

Accidental spills of potentially contaminated material should be decontaminated immediately by covering liberally with a disinfectant solution (0.05% hypochlorite, 5% peroxide, or 1:100 solution of Lysol). All biohazardous waste should be decontaminated by autoclaving. Contaminated equipment or instruments may be decontaminated with a hypochlorite solution, hydrogen peroxide, peracetic acid, 1% glutaraldehyde solution, formaldehyde, ethylene oxide, copper irradiation, or other O.S.H.A. approved solutions, or by autoclaving or boiling for 10 minutes.

VII. **Treatment**

A. Acute Q Fever

Pneumonia usually resolves without treatment in 15 days; therefore, in the event of a bioterrorist attack, therapy may only be required for persons with more severe illness. Several antibiotics have been evaluated as therapeutic agents for acute Q fever -- tetracyclines have been shown to shorten the duration of illness and are considered the **drug of choice**, particularly for severe infection:

- ***Adult dosages:***

  Doxycycline 100 mg every 12 hours po or IV for 15-21 days or **tetracycline** 500 mg po every 6 hours for 15-21 days. (**NOTE:** For milder illnesses, 5-7 days of therapy may be sufficient)

  Alternatives:
  Quinolones, chloramphenicol, trimethroprim-sulfamethoxazole are also probably effective.

  Studies of erythromycin (500 mg - 1 gram every 6 hours p.o. or IV) have shown conflicting results, and erythromycin is probably not preferred for cases of severe pneumonia. Azithromycin appears to be another option but little clinical information is available. Beta-lactam antibiotics are generally ineffective.

- ***Pediatric dosages:***

For more severe illnesses, when benefits outweigh the risks, consider use of doxycycline (or co-trimoxazole or chloramphenicol).

If > or = 8 years of age:
Doxycycline: If > or = 45 kg - 100 mg orally every 12 hours
If < 45 kg - 2.2 mg/kg orally every 12 hours

If < 8 years of age:
Co-trimoxazole: 4 mg/kg orally every 12 hours
Chloramphenicol: 25 mg/kg orally every 12 hours

Newborns up to age 2 months:
Ciprofloxacin: 10-20 mg/kg orally twice daily, do not exceed 1 gram/day.

- ***Pregnant Women Post-Exposure Prophylaxis*** - Co-trimoxazole [1 DS tablet orally twice daily], is the preferred antibiotic, except at term, when the risk of kernicteris is greatest -- use fluoroquinolones [ciprofloxacin 500 mg orally twice daily]

B. Chronic Q Fever

Endocarditis requires combination therapy, usually with doxycycline plus rifampin or possibly a quinolone plus rifampin. The duration of therapy is for years and a valve replacement is often necessary.

VIII. Isolation of Patients

Q fever is not transmissible from person-to-person. Standard precautions should be followed for all patients. Respiratory isolation rooms are not required.

IX. Disposal of Infectious Waste

Use of tracking forms, containment, storage, packaging, treatment and disposal methods should be based upon the same rules as all other regulated medical wastes.

X. Autopsy and Handling of Corpses

All postmortem procedures are to be performed using Universal Precautions.

Efforts should be made to avoid aerosolization.

- All persons performing or assisting in postmortem procedures must wear

mandated P.P.E. (personal protective equipment) as delineated by O.S.H.A. guidelines.

- Instruments should be autoclaved or sterilized with a 10% bleach solution or other solutions approved by O.S.H.A. Surfaces contaminated during postmortem procedures should be decontaminated with an appropriate chemical germicide such as 10% hypochlorite or 5% phenol (carbolic acid).

XI. **Management of Exposed Persons**

An exposed person is defined as a person who has been exposed to the release of a *Coxiella burnetii* containing aerosol.

Post-exposure prophylaxis: Antibiotic prophylaxis is very effective and will prevent clinical disease **if administered 8-12 days AFTER exposure** (doxycycline 100 mg po every 12 hours or tetracycline 500 mg po every 6 hours) for 5 days. **Starting prophylaxis immediately after exposure can delay onset of disease but not prevent symptoms from occurring.**

Pediatric Post-Exposure Prophylaxis with Doxycycline:

If > or = 8 years of age:
Doxycycline: If > or = 45 kg - 100 mg orally every 12 hours for 5 days
If < 45 kg - 2.2 mg/kg orally every 12 hours for 5 days

If < 8 years of age:
Co-trimoxazole: 4 mg/kg orally every 12 hours for 5 days
Chloramphenicol: 25 mg/kg orally every 12 hours for 5 days

Newborns up to age 2 months:
Ciprofloxacin: 10-20 mg/kg orally twice daily for 5 days,
do not exceed 1 gram/day.

XII. Reporting to the Health Department

Q Fever is a reportable disease in California. All suspect cases must be reported immediately to STANISLAUS COUNTY PUBLIC HEALTH SERVICES **by telephone:**

- **During business hours**
  - Call STANISLAUS COUNTY PUBLIC HEALTH SERVICES at 209-558-5678
- **After business hours**
  - Call 209-664-6032 and request the "On Duty Communicable Disease (CD) Staff person."

XIII. References

Byrne WR. Q Fever. In: Sidell FR, Takafuji ET, Franz DR, eds. Medical Aspects of Chemical and Biological Warfare. Washington, D.C.:Office of the Surgeon General, 1997:523-537.

Fleming DO, Richardson JH, Tulis JJ, Vesley D, eds. *Laboratory Safety Principles and Practices* . 2nd ed. Washington, DC: American Society for Microbiology;1995:324.

Marrie TJ. Coxiella burnetii (Q Fever) In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases* 4th ed. New York: Churchill Livingstone;1995:1727-1734.

Raoult D, Marrie T. Q Fever. Clin Infect Diseases 1995;20:489-496.

Raoult D. Treatment of Q Fever. Antimicrob Agents Chemother 1993;37:1733-1736.

Turnbull PCB, Kramer JM. Bacillus. In: Balows A, Haulser WJ, Herrman KL, Shadomy HJ, eds. *Manual of Clinical Microbiology* 5th ed. Washington, DC: American Society for Microbiology; 1991:298-299.

JUNE 2003 (Used with permission and adapted from Santa Clara County Health Department and Merced County Department of Public Health)

Stanislaus County HEALTH SERVICES AGENCY

SMALLPOX

ALL SUSPECT CASES OF SMALLPOX MUST BE REPORTED IMMEDIATELY TO THE PUBLIC HEALTH SERVICES COMMUNICABLE DISEASE CONTROL UNIT:

During business hours: 209-558-5678
After hours: 209-664-6032

Epidemiology:

- Highly infectious after aerosolization
- Person-to-person transmission can occur via droplet nuclei or aerosols expelled from the oropharynx and by direct contact
- Contaminated clothing or bed linens can also spread the virus
- About 30% of susceptible contacts will become infected

Clinical:

- Incubation period is 12-14 days (ranges 7-17 days)
- Characteristic rash appears 2-3 days after nonspecific, flu-like prodrome (fever and headache)
- Maculopapular rash begins on mucosa of mouth and pharynx, face, hands, forearms and spreads to legs and centrally to trunk; lesions are more predominant on the face and extremities than on the trunk.
- Lesions progress synchronously on any given part of the body from macules to papules to vesicles to pustules to crusty scabs

Laboratory Diagnosis:

- Mask and gloves should be worn by person obtaining specimen, preferably a person who has been recently vaccinated
- Vesicular fluid is obtained by opening lesions with the blunt edge of a scalpel, harvesting fluid with a cotton swab; scabs can be removed by forceps. Swabs and scabs should be placed in a vacutainer, sealed with tape, and placed in a second, durable, watertight container
- Laboratory specimens must be handled in a Biosafety Level 4 facility (e.g. CDC) and will be evaluated with electron microscopy and cell culture

Patient Isolation:

- Strict isolation in negative pressure room (high efficiency particulate air filtration ideal) from onset of rash until all scabs separate
- Laundry and waste should be autoclaved before being laundered or incinerated

Treatment:

- Supportive care is the mainstay of therapy
- In-vitro antiviral activity against poxviruses has been shown with adefovir, cidofovir, dipivoxil, and ribavirin. (Animal studies suggest that cidofovir may be most effective).

Prophylaxis:

- Smallpox vaccine would be required for all persons exposed at the time of the bioterrorist attack or anyone with close personal contact with a smallpox case
- Vaccine is most effective if given before or within 3 days of exposure
- Ideally, all exposed persons should be placed in strict quarantine for 17 days after last contact with a smallpox case

Medical Treatment and Response to Suspected Smallpox: Information for Health Care Providers During Biologic Emergencies March 2003

ALL SUSPECT CASES OF SMALLPOX MUST BE REPORTED IMMEDIATELY TO STANISLAUS COUNTY PUBLIC HEALTH SERVICES:

During Business Hours:

209-558-5678

After Hours (Nights, Weekends and Holidays):

209-664-6032

I. KEY SUMMARY POINTS

Epidemiology:

- Highly infectious after aerosolization
- Person-to-person transmission can occur via droplet nuclei or aerosols expelled from the oropharynx and by direct contact
- Contaminated clothing or bed linens can also spread the virus
- About 30% of susceptible contacts will become infected

Clinical:

- Incubation period is 12-14 days (ranges 7-17 days)
- Characteristic rash appears 2-3 days after nonspecific, flu-like prodrome (fever and headache)
- Maculopapular rash begins on mucosa of mouth and pharynx, face, hands, forearms and spreads to legs and centrally to trunk; lesions are more predominant on the face and extremities than on the trunk.
- Lesions progress synchronously on any given part of the body from macules to papules to vesicles to pustules to crusty scabs

Laboratory Diagnosis:

- Mask and gloves should be worn by person obtaining specimen, preferably a person who has been recently vaccinated
- Laboratory specimens must be handled in a Biosafety Level 4 facility (e.g. CDC) and will be evaluated with electron microscopy and cell culture
- Vesicular fluid is obtained by opening lesions with the blunt edge of a scalpel, harvesting fluid with a cotton swab; scabs can be removed by forceps. Swabs and scabs should be placed in a vacutainer, sealed with tape, and placed in a second, durable, watertight container

Patient Isolation:

- Strict isolation in negative pressure room (high efficiency particulate air filtration ideal) from onset of rash until all scabs separate
- Laundry and waste should be autoclaved before being laundered or incinerated

Treatment:

- Supportive care is the mainstay of therapy
- In-vitro antiviral activity against poxviruses has been shown with adefovir, cidofovir, dipivoxil, and ribavirin. (Animal studies suggest that cidofovir may be most effective).

Prophylaxis:

- Smallpox vaccine would be required for all persons exposed at the time of the bioterrorist attack or anyone with close personal contact with a smallpox case
- Vaccine is most effective if given before of within 3 days of exposure
- Ideally, all exposed persons should be placed in strict quarantine for 17 days after last contact with a smallpox case

---

ALL SUSPECT CASES OF SMALLPOX MUST BE REPORTED IMMEDIATELY TO STANISLAUS COUNTY PUBLIC HEALTH SERVICES

During Business Hours:

209-558-5678

After Hours (Nights, Weekends and Holidays):

209-664-6032

II. Introduction/Epidemiology

Smallpox is caused by an Orthopoxvirus, variola, a large enveloped DNA virus. The last occurrence of endemic smallpox was in Somalia in 1977 and the last human cases were laboratory-acquired infections in 1978. Smallpox was declared eradicated in 1980 by the World Health Organization.

Variola is infectious only for humans; there is no animal reservoir. Other key epidemiologic points include:

- The virus is highly stable and retains infectivity for long periods outside the host. Historically, smallpox was more common in the winter and spring; with aerosol infectivity decreasing with higher temperatures and humidity.

- Approximately 30% of susceptible contacts became infected during the era of endemic smallpox.

- Smallpox is transmitted by respiratory secretions, most efficiently during the early stages of the rash illness; it is generally believed that close person-to-person proximity is required for reliable transmission to occur. Patients are considered infectious from the time of development of the eruptive exanthem (usually 2-3 days after fever begins) until all scabs separate. In addition, virus can readily be recovered from scabs throughout convalescence.

- Fomites and inanimate objects are considered potential vehicles of transmission. However, since laundry from infected patients may contain viable virus, bedding and clothing of smallpox patients should be autoclaved.

- **Patients with confirmed or suspected smallpox should be placed on strict isolation until no longer considered infectious.**

- **Strict quarantine with respiratory isolation for 17 days is recommended for all persons in direct contact with a case.** In the setting of a large outbreak due to bioterrorism, this may not be possible - in which case, quarantine of exposed persons in their home with a daily fever watch may be an alternative public health measure.

During the past century, the prototypical disease, variola major, caused mortality of 3% and 30% in the vaccinated and unvaccinated, respectively. The key to control and eventual eradication of endemic smallpox was vigorous case identification, followed by quarantine and immunization of contacts. Routine smallpox vaccination was discontinued in the United States in 1972. Immunity from prior smallpox vaccination wanes with time and at this point, the entire United States' civilian population is likely susceptible. However, persons who have been vaccinated in the past may experience less severe disease.

III. Significance as a Potential Bioterrorist Agent

- High aerosol infectivity; stability of virus in aerosols
- Infectious dose is thought to be low (as low as a few virions)
- Increasing susceptibility of the population
- High mortality rate in the non-immune
- Potential for significant ongoing transmission due to secondary spread
- Ease of large-scale virus production
- Existence of clandestine smallpox virus stockpiles outside the stockpiles at the Centers for Disease Control and Prevention (USA) and the State Center for Virology and Biotechnology (Koltsovo, Russia).
- Currently, worldwide supplies of smallpox vaccine are limited

IV. Clinical Manifestations

During an act of bioterrorism, release of an aerosol will be the most likely route of transmission.

A. Variola major

Incubation period - typically 12-14 days, can be 7-17 days

Symptoms:

Prodrome:

- Acute onset of malaise, fever, rigors, vomiting, headache and backache.
- 15% develop delirium.
- 10% of light-skinned patients have an erythematous rash.

Exanthem:

- Appears as soon as 2-3 days after prodrome, just as fever peaks.
- Discrete maculopapular rash on face, hands, forearms, and mucous membranes of mouth and pharynx. Involvement of palms and soles is common.
- Rash spreads to legs and then centrally to trunk during Week 2.
- Lesions quickly progress from macules to papules to vesicles to pustular vesicles (umbilicated) to crusty scabs.
- Scabs form 8-14 days after onset, leaving depressions and depigmented scars primarily on the face which has more sebaceous glands.

CLINICAL CLUES TO DISTINGUISH SMALLPOX FROM CHICKENPOX:

- Smallpox has many more lesions on face and extremities than trunk (Centrifugal spread).
- Smallpox lesions are synchronous in their stage of development.
- Smallpox lesions are more common on palms and soles.
- Smallpox lesions are more deeply imbedded in the dermis compared with the superficial lesions of chickenpox.

B. Variations in Variola Major

Flat-type/"malignant" smallpox: Occurs in 2-5% of smallpox cases due to lack of adequate cell-mediate immune response. Notable for severe systemic toxicity and slow evolution of flat, soft, focal skin lesions. These papules coalesce and never become pustular. Skin develops a fine-grained reddish color, resembling crepe rubber. The mortality among unvaccinated persons is 95%.

Hemorrhagic-type smallpox: Occurs in < 3% of smallpox cases. Notable for extensive petechia, mucosal hemorrhage and intense toxemia (high fevers, headache, backache and abdominal pain). Seen more commonly in pregnant women. Patients usually die before development of typical pox lesions. Differential diagnosis includes: meningococcemia and acute leukemia.

C. Variola minor (alastrim)

Incubation period - usually 7-17 days

Symptoms - Clinically resembles variola major but with milder systemic toxicity and sometimes more diminutive pox lesions. Lesions on the face are typically more sparse and evolve more rapidly than those on the arms and legs. Mortality in the unvaccinated is usually less than 1%.

D. Clinical Complications of Smallpox

Arthritis and osteomyelitis:	Frequency is 1-2%. Occurs late in course; usually affects children; bilateral elbow joint involvement most common.
Cough and bronchitis:	Occasionally a prominent symptom. Pneumonia was unusual.
Pulmonary edema:	Common in hemorrhagic and flat-type smallpox.
Orchitis:	Noted in 0.1% of patients.
Encephalitis:	Developed in 1 in 500 patients with variola major.
Keratitis / corneal ulcers:	Progresses to blindness in about 1% of cases.
Disease during pregnancy:	Precipitated high perinatal mortality.

E. Monkeypox

A naturally-occurring relative of variola, monkeypox virus, is a rare zoonosis that occurs in the rain forest areas of Africa and is felt to be rodent borne. The disease it causes, monkeypox, is clinically indistinguishable from smallpox, except for notable swelling of cervical and inguinal lymph nodes.

V. **Laboratory Diagnosis**

If smallpox infection is suspected, please *immediately* call Stanislaus County PUBLIC HEALTH SERVICES at 209-558-5678 to arrange for submission of specimens to an appropriate reference laboratory for confirmatory testing. After hours call 209-664-6032 and request the "On Duty Communicable Disease (CD) Staff person."

The diagnosis of smallpox requires astute clinical evaluation. The clinical diagnosis may be confused with chickenpox, erythema multiforme with bullae or allergic contact dermatitis.

The diagnosis of smallpox is an international emergency and confirmation of the diagnosis by laboratory techniques requires coordination between the medical and laboratory community and local, state, federal and international agencies. **If you clinically suspect even a single case of smallpox, notify Stanislaus County PUBLIC HEALTH SERVICES IMMEDIATELY at 209-558-5678 (AFTER HOURS CALL 209-664-6032).**

In the event of a bioterrorist release of smallpox, confirmation by a reference laboratory will be necessary for the earliest (index) cases. After a smallpox outbreak is confirmed, diagnosis of subsequent cases will need to be based on a compatible clinical presentation.

Opening the lesions with the blunt edge of a sterile scalpel and harvesting the fluid with a sterile swab should obtain vesicular fluid. The swab(s) should be placed in a cryo-safe 1-2 ml gasketed vial (the gasket on the vial prevents gas exchange, e.g., carbon dioxide vapors from dry ice, which can acidify samples). Scabs can be removed with forceps and also placed in a gasketed vial. The vial should not contain any transport medium. In addition, a droplet of vesicular fluid can be placed on a clean microscopic slide and allowed to air dry in a safe location. The slides should be placed in an airtight container. Specimens from different patients should not be mixed together. All specimens should be safely secured for shipping. Specimens will be tested at the CDC's Biosafety Level 4 reference laboratory using the following tests:

- **Light or Electronic Microscopy**

Scrapings of vesicular lesions can be examined by electron microscopy for characteristic brick-shaped virions. This method does not distinguish variola from vaccinia, monkeypox or cowpox.

- **Viral cultures**
  Requires isolation of virus and characterization of its growth on chorioallantoic membrane or cell culture.

- **Other Testing**
  Polymerase chain reaction and restriction fragment length polymorphisms (RFLP) diagnostic techniques promise a more accurate and less cumbersome method of identifying variola virus. These techniques are currently only available at national reference laboratories, such as the CDC.

VI. Handling Laboratory Specimens

All other laboratory tests should be performed in Biological Safety Level 2 cabinets and blood cultures should be maintained in a closed system. Laboratory staff handling specimens from persons who might have smallpox must wear surgical gloves, protective gowns and shoe covers. Every effort should be made to avoid splashing or creating an aerosol, and protective eye wear and masks should be worn if work cannot be done in a Biological Safety Level 2 cabinet. A full-face mask respirator with a HEPA (high efficiency particulate air) filter is an acceptable, but cumbersome, alternative to masks and protective eye wear. Laboratories working with a large amount of viral organisms should use Biological Safety Level 3 cabinets.

Accidental spills of potentially contaminated material should be decontaminated immediately by covering liberally with a disinfectant solution (1% sodium hypochlorite or sodium hydroxide (0.1N)). All biohazardous waste should be decontaminated by autoclaving. Contaminated equipment or instruments may be decontaminated with a hypochlorite solution, 1% peracetic acid, formaldehyde, ethylene oxide, copper irradiation, or other O.S.H.A. approved solutions, or by autoclaving or boiling for 10 minutes.

VII. Treatment

Supportive care is the mainstay of therapy.

Currently, there are no anti-viral drugs of proven efficacy. Although, adefovir, dipivoxil, cidofovir and ribavirin have significant in vitro antiviral activity against poxviruses, their efficacy as therapeutic agents for smallpox is currently uncertain. Cidofovir is FDA licensed and shows the most promise in animal models.

VIII. **Isolation of Patients**

Smallpox is transmissible from person-to-person by exposure to respiratory secretions (particularly from coughing patients), contact with pox lesions and by fomites (although not efficiently). All staff should observe **both Airborne and Contact Precautions**, in addition to Standard Precautions, when caring for patients with suspected or confirmed smallpox.

Patients should be placed in a closed-door, negative pressure room with 6 to 12 air exchanges per hour and HEPA filtration of exhausted air. Patients with smallpox should be placed on strict isolation from the onset of eruptive exanthem until all pox scabs have separated (generally 14-28 days). Healthcare workers and others entering the room should wear appropriate respiratory protection; respiratory masks should meet the minimal NIOSH standard for particulate respirators (N95). Healthcare provides should wear clean gloves and gowns for all patient contact.

In the event of a large-scale smallpox outbreak due to a bioterrorist attack, there may be massive numbers of victims. In this case, there may be a need to cohort patients due to limited availability of respiratory isolation rooms. If this is done, then all patients should receive smallpox vaccine or vaccine immune globulin within 3 days of exposure, if available, in the event that some of these patients are misdiagnosed with smallpox.

All healthcare workers providing direct patient care to persons with smallpox should be vaccinated. If vaccine is unavailable, then only staff who previously received smallpox vaccine (*e.g., persons born before 1972 or persons who were in the military before 1989*) should be caring for patients with smallpox.

IX. **Disposal of Infectious Waste**

Use of tracking forms, containment, storage, packaging, treatment and disposal methods should be based upon the same rules as all other regulated medical wastes.

X. **Autopsy and Handling of Corpses**

All postmortem procedures are to be performed using Universal Precautions. In addition, due to concerns about aerosolization of the virus, personnel should use particulate respirators as recommended under **Strict Isolation** precautions.

- All persons performing or assisting in postmortem procedures must wear mandated P.P.E. (personal protective equipment) as delineated by O.S.H.A. guidelines.

- Instruments should be autoclaved or sterilized with a 10% bleach solution or other solutions approved by O.S.H.A. Surfaces contaminated during postmortem procedures should be decontaminated with an appropriate chemical germicide such as 10% hypochlorite or 5% phenol (carbolic acid).

XI. **Management of Exposed Persons**

An exposed person is defined as a person who has been in close personal contact with a patient with suspect or confirmed smallpox. **Close personal contact** includes persons residing in the same household with the case-patient or persons with face-to-face contact with the case AFTER the case developed febrile illness. (During outbreaks in Europe in the 1960's, up to 10-20 secondary cases occurred after exposure to a single case-patient, if vaccination efforts were delayed.)

- **Quarantine**: All exposed persons should be placed in strict quarantine with respiratory isolation for 17 days after last contact with suspect or confirmed smallpox case(s). In the setting of a large outbreak due to bioterrorism, this may not be possible - in which case, quarantine of exposed persons in their home with a daily fever watch may be an alternative public health measure.

- **Vaccination**:
  Vaccine: In the United States, the smallpox vaccine supply is overseen by the

CDC. The Wyeth vaccine (using the New York Board of Health vaccinia strain) is freeze-dried in multidose vials (50 doses per vial) at 20°C.

Vaccine Indications: All exposed persons, including all household and face-to-face contacts of patients, should be vaccinated immediately, if vaccine is available. Additionally, all health care workers that might care for smallpox patients, emergency personnel who might transport patients, and mortuary staff should be vaccinated, if vaccine is available. **Vaccination is most effective at protecting against smallpox if given within 3 days of exposure.**

Methodology: A bifurcated needle is inserted into an ampule of reconstituted vaccine and, on withdrawal, a droplet of vaccine is held by capillarity between the two tines. The needle is held at right angles to the skin, the wrist of the vaccinator rests against the arm. Fifteen up and down (perpendicular) strokes of the needle are rapidly made in an area of 5-mm diameter. The strokes should be sufficiently vigorous so that a trace of blood appears at the vaccination site after 15-30 seconds. Excess vaccine should be wiped from the site with gauze (gauze should be discarded into a hazardous waste receptacle) and the site covered with a loose, non-occlusive bandage.

Evaluation of vaccine response:

(1) Primary vaccine response (never previously vaccinated):

Day 3: A red papule appears at the vaccination site

Day 5: Papule becomes vesicular

Day 7: A whitish, umbilicated, multilocular pustule develops, containing turbid lymph and surrounded by an erythematous areola which may expand further for 3 days. Fever during days 4-14, particularly for children, is common. The pustule dries and falls off after about 3 weeks.

(2) Re-immunization response (those previously vaccinated):

May react asdescribed above, or may have a papule surrounded by erythema that peaks between 3 and 7 days. A response that peaks within 48 hours is a hypersensitivity reaction; patients with this reaction should be revaccinated.

- **Contraindications to Vaccination**:
  - Eczema or other exfoliative skin condition (*e.g., atopic dermatitis, burns, impetigo*)
  - Leukemia, lymphoma, generalized malignancy or chemotherapy with alkylating agents, antimetabolites, radiation or high dose corticosteroids
  - HIV infection or AIDS
  - Hereditary immune deficiency disorders
  - Pregnant women
  - Life-threatening allergy to polymyxin B, streptomycin, tetracycline or neomycin.

In the setting of a large bioterrorist attack, the risk of vaccination must be weighed against the likelihood of acquiring infection. If VIG (vaccinia immune globulin) is available, those in close personal contact with a smallpox case AND with a clear contraindication to vaccine may receive vaccine PLUS VIG (0.3 ml/kg of body weight) simultaneously within the first week following exposure.

- **Potential Side-Effects of Vaccination**:

Side effects include: low grade fever, lymphadenopathy, autoinoculation, secondary inoculation, ocular vaccinia, urticarial rash, Stevens-Johnson syndrome, generalized vaccinia (3 per 10,000 vaccinations occurring from 6-9 days after vaccination), eczema vaccinatum, progressive vaccinia (1 per million vaccinations) and postvaccinial encephalitis (3 per million primary vaccinations occurring from 8-15 days after vaccination).

Severe vaccine complications should be treated with VIG (0.6 ml/kg body weight). The dose should be administered intramuscularly in 2 divided doses over a 24 to 36 hour period. The dose can be repeated in 2-3 days, if needed.

XII. **Reporting to the Health Department**

Smallpox is an international emergency and even an isolated suspect case must be reported immediately to Stanislaus County PUBLIC HEALTH SERVICES.

All suspect cases should be immediately reported **by telephone**:

- **During business hours**
  - Call Stanislaus County PUBLIC HEALTH SERVICES at 209-558-5678
- **After business hours**
  - Call 209-664-6032 and request the "On Duty Communicable Disease (CD) Staff person."

XIII. **References**

Breman JG, Henderson DA. Poxvirus dilemmas -- monkeypox, smallpox and biological terrorism. New Engl J Med 1998;339:556-559.

Esposito JJ, Massung RF. Poxvirus infections in humans. In: Murray PR, Tenover F, Baron EJ, eds. Clinical Microbiology. Washington: American Society for Microbiology, 1995:1131-1138.

Goldstein VA, Neff JM, Lande JM, Koplan JP. Smallpox vaccination reactions, prophylaxis and therapy of complications. Pediatrics 1975;55:342-347.

Henderson DA, Inglesby TV, Bartlett JG, et al. Smallpox: Civilian medical and public health management following use of a biological weapon. Consensus statement of the Working Group on Civilian Biodefense. JAMA 1999.

Lane JM, Ruben FL, Neff JM, Millar JD. Complications of smallpox vaccination, 1968: National surveillance in the United States. New Engl J Med 1969;281:1201-1208. Mack TM. Smallpox in Europe, 1950-1971. JID 972;125:161-169.

US Army Medical Research Institute of Infectious Diseases. Medical Management of Biological Casualties. 3rd Edition. Fort Detrick, MD. 1998.

JUNE 2003 (Used with permission and adapted from Santa Clara County Health Department and Merced County Department of Public Health)

Stanislaus County HEALTH SERVICES AGENCY

TULAREMIA

ALL SUSPECT CASES OF TULAREMIA MUST BE REPORTED IMMEDIATELY TO PUBLIC HEALTH SERVICES COMMUNICABLE DISEASE CONTROL UNIT:

During business hours: 209-558-5678
After hours : 209-664-6032

Epidemiology:

- Highly infectious after aerosolization
- Infectious dose can be as low as 10-15 organisms
- Person-to-person transmission does not occur

Clinical:

- Incubation period is 3-6 days (ranges 1-21 days)
- Aerosolization would most likely result in typhoidal tularemia, with pneumonic involvement
- Typhoidal tularemia is a nonspecific illness, with fever, headache, malaise and non-productive cough (mortality rates can be as high as 30-60%)
- Diagnosis requires high index of suspicion given nonspecific presentation

Laboratory Diagnosis:

- Bacterial cultures should be handled in a Biosafety Level 3 facility; isolation of organism can otherwise put laboratory workers at risk
- Organism is difficult to culture and grows poorly on standard media; cysteine-enriched media is required
- Serology is most commonly used for diagnosis

Patient Isolation:

- Universal precautions. Respiratory isolation not required.

Treatment:

- Streptomycin (7.5 mg/kg IM q 12 hours x 10-14 days) or gentamicin (3-5 mg/kg/day IV or IM qd in 3 divided doses x 10-14 days) are the preferred antibiotics
- Tetracyclines are alternative choices, although they are bacteriostatic and associated with higher relapse rates and must be continued for at least 14 days

Prophylaxis:

- Antibiotic prophylaxis is most effective if begun within 24 hours after exposure to aerosol
- Tetracyclines are recommended for 14 days

Medical Treatment and Response to Suspected Tularemia: Information for Health Care Providers During Biologic Emergencies March 2003

ALL SUSPECT CASES OF TULAREMIA MUST BE REPORTED IMMEDIATELY TO STANISLAUS COUNTY PUBLIC HEALTH SERVICES:

During Business Hours:

209-558-5678

After Hours (Nights, Weekends and Holidays):

209-664-6032

I. KEY SUMMARY POINTS

Epidemiology:

- Highly infectious after aerosolization
- Infectious dose can be as low as 10-15 organisms
- Person-to-person transmission does not occur

Clinical:

- Incubation period is 3-6 days (ranges 1-21 days)
- Aerosolization would most likely result in typhoidal tularemia, with pneumonic involvement
- Typhoidal tularemia is a nonspecific illness, with fever, headache, malaise and non-productive cough (mortality rates can be as high as 30-60%)
- Diagnosis requires high index of suspicion given nonspecific presentation

Laboratory Diagnosis:

- Bacterial cultures should be handled in a Biosafety Level 3 facility; isolation of organism can otherwise put laboratory workers at risk
- Organism is difficult to culture and grows poorly on standard media; cysteine-enriched media is required
- Serology is most commonly used for diagnosis

Patient Isolation:

- Standard precautions. Respiratory isolation not required.

Treatment:

- Streptomycin (7.5 mg/kg IM q 12 hours x 10-14 days) or gentamicin (3-5mg/kg/day IV or IM qd in 3 divided doses x 10-14 days) are the preferred antibiotics

- Tetracyclines are alternative choices, although they are bacteriostatic and associated with higher relapse rates and must be continued for at least 14 days

Prophylaxis:

- Antibiotic prophylaxis is most effective if begun within 24 hours after exposure to aerosol

- Tetracyclines are recommended for 14 days

ALL SUSPECT CASES OF TULAREMIA MUST BE REPORTED IMMEDIATELY TO STANISLAUS COUNTY PUBLIC HEALTH SERVICES

During Business Hours:

209-558-5678

After Hours (Nights, Weekends and Holidays):

209-664-6032

II. Introduction/Epidemiology

Tularemia is a zoonotic disease caused by *Francisella tularensis,* a gram-negative intracellular coccobacillus. *F. tularensis* has several biovars; *F. tularensis* biovar *tularensis* is the most common naturally-occurring isolate in the United States. The organism is primarily recovered from lagomorphs (rabbits), rodents and arthropods (ticks and deer flies) in the United States and from water, mosquitoes and aquatic mammals outside the United States. The rabbit is the vertebrate most commonly associated with tularemia in North America. In recent years, the reported incidence of tularemia has declined to less than 200 cases per year in the United States.

Tularemia is acquired under natural conditions by direct inoculation (such as an arthropod bite), animal contact such as skinning or eating infected animals, or via the airborne route. (Domestic cats have occasionally transmitted tularemia by bites or scratches.) *F. tularensis* may survive for prolonged periods in water, mud and animal carcasses; even if frozen *Francisella tularensis* is highly infectious. After aerosolization,

10-50 virulent organisms given by aerosol can cause infection in humans, and as few as 10 organisms can cause infection when administered percutaneously. In the event of a bioterrorist attack, aerosolization would be the most likely route of infection.

Tularemia transmission from patient-to-patient has never been reported, even among patients with tularemia pneumonia. Persons exposed to an aerosol of *Francisella tularensis* do not present a risk for secondary infection of others or for re-aerosolization of the organism.

III. Significance as a Potential Bioterrorist Agent

- Weaponized by the United States military during the biologic offensive program in the 1950s-1960s.
- Highly infectious after aerosolization; infectious dose can be as low as 10 to 50 microorganisms if inhaled.
- Aerosolized *F. tularensis* would cause typhoidal tularemia (a nonspecific, febrile illness), with high mortality rates (30-60%) if untreated.

IV. Clinical Manifestations

During an act of bioterrorism, release of an aerosol will be the most likely route of transmission with typhoidal tularemia the most likely clinical presentation..

There are several different classification systems for clinical tularemia. The most straightforward classifies tularemia into ulceroglandular (75% of patients) and typhoidal (25% of patients). **Ulceroglandular** disease involves lesions on the skin or mucous membranes (including conjunctiva), lymph nodes larger than 1 cm, or both. In **typhoidal** tularemia, the lymph nodes are usually smaller than 1 cm and no skin or mucous membrane lesions are present--this form is more commonly associated with pneumonia and has a higher mortality rate.

A. *Typhoidal Tularemia* -- An acute, nonspecific febrile illness associated with *F. tularensis* that is **not** associated with prominent lymphadenopathy. Typhoidal tularemia is mainly due to inhalation of infected aerosols. **Most likely form during an act of bioterrorism.**

Incubation period: 3 - 6 days (range 1- 21 days)

Symptoms - prominent symptoms include:

- fever with chills
- headache
- myalgias
- sore throat
- anorexia
- nausea
- vomiting
- diarrhea (can be a major component of illness, generally watery stool not bloody)
- abdominal pain
- cough

Patients may develop a sepsis syndrome with hypotension, adult respiratory distress syndrome, renal failure, disseminated intravascular coagulation and shock.

Pleuropulmonary disease (pneumonic tularemia) is common with pulmonary infiltratesor pleural effusions seen in up to 45% of typhoidal tularemia cases. A patchy, alveolar process is most often seen on chest x-ray. Patients may develop acute respiratory distress syndrome and require mechanical ventilation.

B. *Ulceroglandular Tularemia* -- generally due to inoculation of the organism into the skin or mucous membranes.

Incubation period: 3 - 6 days (range 1 - 21 days)

Symptoms - Local papule develops at the inoculation site, with progression to a pustule then an ulcer within several days. Lymphadenopathy develops in 85% of patients. Nodes are usually tender and 0.5-10 cm in diameter (mean 2 cm). Enlarged nodes may become fluctuant, drain spontaneously or persist for months to years.

A cutaneous ulcer occurs in 60% of cases. Ulcers are usually singular and 0.4-3.0 cm in diameter, with heaped-up borders. Ulcers are almost always accompanied by regional lymphadenopathy.

In addition, the following symptoms may be present (in decreasing order of likelihood of

appearance):

- fever (present in 85% of patients)
- chills
- headache
- cough
- myalgia
- chest pain
- vomiting
- arthralgia
- sore throat
- abdominal pain
- diarrhea
- dysuria
- back pain
- stiff neck

Ulceroglandular tularemia can also be complicated by pleuropulmonary disease or pharyngeal involvement. Pharyngeal tularemia (via ingestion of contaminated food, water or droplets) is associated with severe throat pain, exudative pharyngitis and often pharyngeal ulcerations.

V. **Laboratory Diagnosis**

Routine laboratory work must be done in Biosafety Level 2 facilities. However, handling of bacterial cultures once the organism is identified should be done in Biosafety Level 3 facilities If tularemia is suspected, please call STANISLAUS COUNTY PUBLIC HEALTH SERVICES Laboratory at 209-558-5678 to arrange for submission of specimens for testing. After hours, please call 209-664-6032.

- **Culture**

  F. tularensis grows poorly on standard media. It forms small, smooth, opaque colonies when grown on media containing cysteine or other sulfhydryl

compounds (*e.g., glucose cysteine blood agar or thioglycollate broth*) at 37C. The organism has also been isolated from automated radiometric detection systems if the media is subcultured on chocolate agar. The bacteria grows slowly; some strains may require up to 2-3 weeks to develop visible colonies. **Notify the clinical laboratory in advance of submitting specimens for culture which may contain *F. tularensis,* since isolation of the organism can put laboratory workers at risk for infection.**

- **Serology**

  Antibody detection assays include tube agglutination, microagglutination and ELISA. Significant antibody does not appear until the end of the second week of illness, peaks at 4-5 weeks, and can persist for more than a decade. A single titre (by tube agglutination) of > 1:160 is a presumptive positive; a four-fold rise is required for a definitive serologic diagnosis. ELISA and microagglutination tests may be more sensitive than tube agglutination. Antibodies may cross-react with *Brucella* spp., *Proteu*s 0X19 and *Yersinia* spp. but dithiothreitol treatment of the serum will eliminate most of these reactions. Serology testing is available through national reference laboratories.

VI. Handling Laboratory Specimens

Tularemia is the third most commonly reported laboratory-associated bacterial infection. Cases have occurred among clinical laboratorians working with bacterial cultures. Laboratory staff handling specimens from persons who are suspected of having tularemia must wear face masks with eye protection, surgical gloves, protective gowns, and shoe covers --- especially when working with pure bacterial cultures. Laboratory tests (*such as serological examinations and staining of impression smears*) can be performed in Biological Safety Level 2 cabinets.

Blood cultures should be maintained in a closed system and clinical isolates from blood or any other site should be handled in Biological Safety Level 3 cabinets. Every effort should be made to avoid splashing or creating an aerosol. Biosafety Level 3 practices and facilities should be used for inoculation, incubation, centrifugation and harvesting of cell cultures and the manipulation of infected tissues. Accidental spills of potentially contaminated material should be decontaminated immediately by covering liberally with a disinfectant solution (0.1% sodium hypochlorite

or sodium hydroxide (0.1N)). All biohazardous waste should be decontaminated by autoclaving. Contaminated equipment or instruments may be decontaminated with a hypochlorite solution, hydrogen peroxide, peracetic acid, 1% glutaraldehyde solution, formaldehyde, ethylene oxide, copper irradiation, or other O.S.H.A. approved solutions, or by autoclaving or boiling for 10 minutes.

VII. **Treatment**

The treatment of choice for all forms of tularemia except meningitis is streptomycin; gentamicin is an acceptable alternative. For both drugs, dosages must be adjusted for renal insufficiency. **Gentamicin is safe during pregnancy; avoid streptomycin due to ts association with irreversible deafness in children exposed in utero.**

(1) **Streptomycin**: Adult dosage is 0.5-1.0 gm (7.5 mg/kg) intramuscularly every 12 hours for 10-14 days. In very sick patients, streptomycin may be give at 15 mg/kg intramuscularly every 12 hours for 10-14 days.
Pediatric dose: 15 mg/kg intramuscularly every 12 hours for 10-14 days.

Alternatives:
(2) **Gentamicin**: 3-5 mg/kg/day intravenously or intramuscularly in three divided doses, with a peak serum level of at least 5 ug/ml desirable. Continue for 10-14 days.
Pediatric dose: 2.5 mg/kg intravenously or intramuscularly every 8 hours for 10-14 days

(3) Tetracycline and chloramphenicol are bacteriostatic and associated with high relapse rates. These agents must be continued for a minimum of 14 days.
Tetracycline: 2 grams /day IV or orally in four divided doses or **doxycycline** 100 mg IV or orally twice a day for at least 14 days.
Pediatric dose: [Not recommended for children less than 9 years, pregnant or lactating women] If > 45 kg, give adult dosage of doxycycline; if less than 45 kg, give 2.2 mg/kg twice a day. Tetracycline at 30 mg/kg/day orally, to a maximum of 2 grams/day, in four divided doses for at least 14 days.

Chloramphenicol should generally not be used due to the availability of effective alternatives with fewer serious side effects.

(4) Additional agents with favorable in vitro susceptibility tests but limited clinical data on efficacy include: fluroquinolones (except cinoxacin), erythromycin (resistant strains of *F. tularensis* have been identified), and rifampin. Penicillin and cephalosporins are not effective and should not be used to treat tularemia.

Meningitis

A rare complication of tularemia, meningitis requires special attention with regard to therapy as the penetration of streptomycin or gentamicin into the CSF is suboptimal. The treatment of meningeal infection should include combination therapy with chloramphenicol plus streptomycin or possibly a third-generation cephalosporin plus streptomycin (limited data available on efficacy).

VIII. Isolation of Patients

Tularemia is not transmissible from person-to-person. Standard precautions should be followed for all patients -- **respiratory isolation rooms are not required**. Ulcers or wounds in patients with tularemia should be covered and contact isolation maintained as *F. tularensis* can be isolated from such lesions for one month or longer.

IX. Disposal of Infectious Waste

Use of tracking forms, containment, storage, packaging, treatment and disposal methods should be based upon the same rules as all other regulated medical wastes.

X. Autopsy and Handling of Corpses

All postmortem procedures are to be performed using Respiratory Precautions. Efforts should be made to avoid aerosolization.

- All persons performing or assisting in postmortem procedures must wear mandated P.P.E. (personal protective equipment) as delineated by O.S.H.A. guidelines.
- Instruments should be autoclaved or sterilized with a 10% bleach solution or other solutions approved by O.S.H.A. Surfaces contaminated during postmortem procedures should be decontaminated with an appropriate chemical germicide such as 10% hypochlorite or 5% phenol (carbolic acid).

XI. Management of Exposed Persons

An exposed person is defined as a person who has been exposed to the release of a *Francisella tularensis*-containing aerosol.

- **Post-exposure prophylaxis**: Antibiotic prophylaxis should begin as soon as possible after exposure and is **most effective if begun within 24 hours**. Limited data suggests that tetracyclines may be effective:
  Tetracycline 500 mg orally in 4 divided doses for 14 days
  Doxycycline 100mg orally twice daily for 14 days

- **Pediatric patients and pregnant women**: Although tetracyclines are not generally recommended for children under age 9 or for pregnant women, the risk of developing tularemia may outweigh these limitations. Floroquinolones are a potential alternative for prophylaxis.
  Doxycycline:
  - If > 45 kg - 100 mg orally every 12 hours
  - If < 45 kg - 2.2 mg/kg orally every 12 hours

If antibiotic prophylaxis is not started within 24 hours of exposure, then exposed persons should be instructed to begin a fever watch and seek medical care if temperature exceeds 38.5 ^{o}C.

XII. Reporting to the Health Department

Tularemia is a reportable disease in California. All suspect cases must be reported immediately to STANISLAUS COUNTY PUBLIC HEALTH SERVICES **by telephone:**

- **During business hours**
  - Call STANISLAUS COUNTY PUBLIC HEALTH SERVICES at 209-558-5678

- **After business hours**
  - Call 209-664-6032 and request the "On Duty Communicable Disease (CD) Staff person."

XIII. References

Enderlin G, Morales L, Jacobe RF, Cross JT. Streptomycin and alternative agents f or the treatment of tularemia: review of the literature. Clin Infect Dis. 1994;19:42-47.

Evans ME, Friedlander AM. Tularemia. In: Sidell FR, Takafuji ET, Franz DR, eds.

Medical Aspects of Chemical and Biological Warfare. Part I. Washington, DC: Office of the Surgeon General at TMM Publications;1997:503-512.

Evans ME, Gregory DW, Schaffner W, McGee ZA. Tularemia: A 30-year experience with 88 cases. Medicine. 1985;64:251-269.

Fleming DO, Richardson JH, Tulis JJ, Vesley D, eds. *Laboratory Safety Principles and Practices* . 2nd ed. Washington, DC: American Society for Microbiology;1995:324.

Franz DR, Jahrling PB, Friedlander AM, et al. Clinical recognition and management of patients exposed to biological warfare agents. JAMA. 1997;278:399-411.

Penn RL. Francisella tularensis (Tularemia). In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases. 4th ed. New York, NY: Churchill Livingston Inc; 1995:2060-2068.

Sawyer WD, Dangerfield HG, Hogge AL, Crozier D. Antibiotic prophylaxis and therapy of airborne tularemia. Bacteriol Rev. 1966;30:542-548.

Turnbull PCB, Kramer JM. Bacillus. In: Balows A, Haulser WJ, Herrman KL, Shadomy HJ, eds. *Manual of Clinical Microbiology* 5th ed. Washington, DC: American Society for Microbiology; 1991:298-299.

JUNE 2003 (Used with permission and adapted from Santa Clara County Health Department and Merced County Department of Public Health)

HEALTH SERVICES AGENCY

VIRAL HEMORRHAGIC FEVERS

ALL SUSPECT CASES OF VIRAL HEMORRHAGIC FEVER MUST BE REPORTED IMMEDIATELY TO PUBLIC HEALTH SERVICES COMMUNICABLE DISEASE CONTROL UNIT:

During business hours: 209-558-5678
After hours : 209-664-6032

Etiologic Agents: Arenaviradae (Lassa, Junin, Machupo, Guanarito, and Sabia), Filoviradae (Marburg and Ebola), Bunyaviradae (Congo-Crimean hemorrhagic fever virus and hantaviruses)and Flaviradae (yellow fever and Dengue) can all cause viral hemorrhagic fever (VHF)

Epidemiology:

- Highly infectious after aerosolization
- Infectious dose can be as low as 1-10 organisms
- Risk of person-to-person transmission depends on virus

Clinical:

- Incubation period is 4 – 21 days, depending on virus
- Clinical presentation would vary by viral agent; however, dominant clinical features of all are a consequence of microvascular damage and changes in vascular permeability. Fever, myalgia, and prostration may evolve to shock, generalized mucous membrane hemorrhage, and neurologic, hematopoietic, or pulmonary involvement.

Laboratory Diagnosis:

- Viral isolation should be handled in a Biosafety Level 3 or 4 facility and may take 3 – 10 days
- ELISA or reverse transcriptase PCR available for most VHF viruses

Patient Isolation:

- Isolation room with contact precautions.

Treatment:

- Ribavirin (30 mg/kg IV x 1, then 15 mg/kg IV q 6 h x 4 days, 7.5 mg/kg IV q 8 x 6 days) may be helpful for Congo-Crimean hemorrhagic fever or arenaviruses

Prophylaxis:

- Licensed vaccine available only for yellow fever