

Plague & Tularemia: Review of Two Tier 1 Select Agents

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Objectives

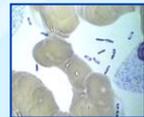
For both plague and tularemia, review:

- Modes of transmission & clinical presentation
- Diagnosis
- Bioterrorism – history, signs of a bioterrorism attack, treatment, response
- CDC activities & resources

PLAGUE: GENERAL INFORMATION

Plague

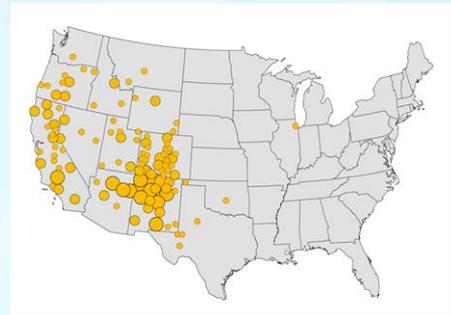
- *Yersinia pestis* – nonmotile, gram-negative bacillus
- Transmitted by:
 - Bites of infected rodent fleas (most common)
 - Handling infected animal tissues
 - Inhaling respiratory droplets from plague-infected animals, including pets
- Person-to-person transmission is possible but uncommon



Human Plague Cases Reported by Country, 2000-2009



Plague in the United States, 1965-2012



1 dot = 1 case, placed randomly within county of occurrence

Clinical Manifestations of Plague

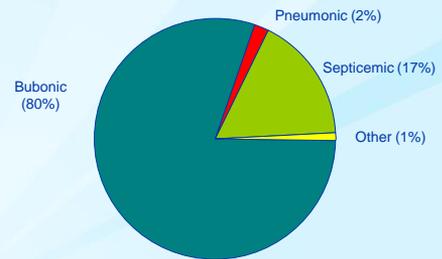
- Bubonic
- Septicemic
- Pneumonic
- Less common forms – pharyngeal, meningial
- 66% mortality prior to availability of antibiotics
- Mortality now 5-14% depending on clinical form



Photo credit: CDC Public Health Image Library



Frequency of Primary Plague Types, United States, 1965-2012



Kugeler et al. Epidemiology of Human Plague in the United States, 1900–2012. EID 2015.

Initial Laboratory Testing for Plague

Collect primary specimen

- Bubo aspirate, blood, or sputum
- Inoculate for culture
 - General microbiologic media (e.g. sheep blood agar)
 - Grows slowly
- Staining
 - Gram-negative coccobacilli
 - Giemsa stain: bipolar staining organisms



Photo credit: CDC

Collect blood for acute and convalescent serology

Peripheral Blood Smear from Patient with Septicemic Plague



Smear shows characteristic bipolar (safety pin) staining of *Y. pestis*
Wright-Giemsa stain; magnification x 1000

Laboratory Testing for Plague - Continued

- Culture
 - Growth ~24-48 hours after inoculation
 - Automated bacterial identification systems may misidentify *Y. pestis*
 - Direct fluorescent antibody testing (F1 antigen detection) for rapid presumptive identification of isolate
 - Phage lysis for definitive identification of *Y. pestis*
- PCR
- Serology
 - Four-fold rise between acute and convalescent samples
 - Convalescent at least 2 weeks after acute sample

CDC research and prevention efforts

Uganda

- Rat control projects
- Treatment trial: doxycycline vs. ciprofloxacin

Plague “Dipstick” (Lateral Flow Assay)

- Rapid
- Inexpensive
- Technically simple
- Guide diagnosis and treatment, reduce the need for culture at remote sites



Recent Events

Morbidity and Mortality Weekly Report

Human Plague — United States, 2015

Narula Kwi, DVM^{1,2}; Christina Nelson, MD³; Karsten Knigler, PhD²; Jeannine Patten, PhD²; Lydia Platts, MSPH¹; Hayley Yaglom, MPH¹; Vicki Kramer, PhD⁴; Benjamin Schwanz, MD⁵; Jonathan House, DVM⁶; Leah Colton, PhD⁷; Amanda Feldsparsh, MPH¹; Christa Demack, DVM¹; Juan Bumbach, MD⁸; Mark DiMenna, PhD⁹; Emily Fisher, MD¹⁰; Emilio DeBos, DVM¹⁰; Danielle Bartke, DVM¹¹; Matthew Weinhorke, MPH¹; Christopher Pevy, MD¹²; Martin Schiefer, PhD¹³; Ken Gager, PhD¹⁴; Paul Mead, MD²

On August 25, 2015, this report was posted as an MMWR Early Release on the MMWR website (<http://www.cdc.gov/mmwr>). Since April 1, 2015, a total of 11 cases of human plague have been reported in residents of six states: Arizona (two), California (one), Colorado (four), Georgia (one), New Mexico (two), and Oregon (one). The two cases in Georgia and California residents have been linked to exposures at or near Yosemite National Park in the southern Sierra Nevada Mountains of California. Nine of the 11 patients were male; median age was 52 years (range = 14–79 years). Three patients aged 16, 52, and 79 years died.

The mortality rate for untreated plague has ranged from 66% to 93%; however, in the antibiotic era, mortality has been reduced to approximately 16% (4). Prompt treatment with antimicrobials such as aminoglycosides, fluoroquinolones, or doxycycline greatly improves outcome (4). Health care providers should consider the diagnosis of plague in any patient with compatible signs or symptoms, residence or travel in the western United States, and recent proximity to rodent habitats or direct contact with rodents or ill domestic animals. Suspicion of plague should prompt 1) collection of blood, bubo aspirate, or sputum samples for *Y. pestis* diag-

Yosemite National Park – 2015

CBS NEWS August 7, 2015, 12:06 PM

Child in California diagnosed with plague

Comment / Share / Tweet / Stumble / Email

Last Updated Aug 7, 2015 7:55 PM EDT

LOS ANGELES – A child in Southern California is recovering after contracting a rare case of plague. It's the first time the disease has been diagnosed in the state in almost a decade, authorities said Thursday.

CBS Los Angeles reports the child – who was identified only as a resident of Los Angeles County – became ill and was hospitalized following a visit to Stanislaus National Forest and camping at Crane Flat Campground in Yosemite National Park in mid-July, according to California Department of Public Health spokeswoman Anita Gore.



Plague Found At Two Yosemite National Park Campgrounds

By Matt Zeman on August 14th, 2015

Plague recently has been found in two campgrounds at Yosemite National Park, including one where a child who contracted the potentially deadly disease had camped.

The Crane Flat Campground, where the unidentified child had stayed in mid-July, was treated for disease-carrying fleas earlier this week. Next week the Tushnet Meadows Campground will be treated by having rodent burrows

Possible Human-to-Human Transmission of Plague

Outbreak of Human Pneumonic Plague with Dog-to-Human and Possible Human-to-Human Transmission – Colorado, June–July 2014

Weekly
May 1, 2015 / 64(18):429–434

Jamira K. Runfola, PhD¹; Jennifer House, DVM²; Lisa Miller, MD³; Leah Colton, PhD⁴; Donna Hill⁵; Alex Weaver¹; Paul Mead, MD²; Martin Schiefer, PhD²; Jeannine Patten, PhD²; Colleen Cascardi, MPH⁶; Kristina H. Strandson, MD⁷; Clayton Fraser, MD⁸; Kristy L. Padonka, DVM, PhD⁹; Gary Hagan, DVM, PhD⁹; John H. Douglas, Jr., MD¹⁰ (Author affiliations at end of text)

On July 8, 2014, the Colorado Department of Public Health and Environment (CDPHE) laboratory identified *Yersinia pestis*, the bacterium that causes plague, in a blood specimen collected from a man (patient A) hospitalized with pneumonia. The organism had been previously misidentified as *Pseudomonas* (specie) by an automated system in the hospital laboratory. An investigation led by TFS County Health Department (TCHD) revealed that patient A's dog had died recently with hemorrhagic. Three other persons who had contact with the dog, one of whom also had contact with patient A, were ill with fever and respiratory symptoms.

Patient	Date of exposure (source)	Onset of illness	Chest radiograph findings
D	June 25 (dog)	July 5	PNA
	June 29 (patient A)		

Local Plague Cases – 2015

Septicemic Plague Kills a Colorado Teen the Day After His Birthday

By Matt Zeman on July 14, 2015



Plague kills Colorado high school student

Local Plague Death Confirmed

Santa Fe County woman died of plague, health department is treating those in contact with her

July 27, 2015, 3:30 pm
By Julie Ann Galanter

PLAGUE: BIOTERRORISM

History of Plague as a Biological Weapon

- **World War II**
 - Japanese Army Unit 731 dropped plague-infected fleas over populated areas of China
- **US and USSR bioweapons programs**
 - Techniques to aerosolize *Y. pestis*
 - US offensive program discontinued in 1970s
 - Soviet program continued through early 1990s

This laptop reveals terror group 'wants to turn bubonic plague into a weapon of war'



<http://foreignpolicy.com/2014/08/28/found-the-islamic-states-terror-laptop-of-doom/>

- **ISIS – August 2014**
 - “The [confiscated] laptop contains a 19-page document in Arabic on how to develop biological weapons and how to weaponize the bubonic plague from infected animals.”

<http://www.independent.co.uk/news/world/middle-east/isis-laptop-reveals-wmd-plans-9702030.html>

Intentional Release of *Y. pestis*

- **1970 World Health Organization (WHO) report**
 - 50 kg of *Y. pestis* released as aerosol
 - Metropolitan area of 5 million
- **Outcomes**
 - 150,000 pneumonic plague cases
 - 36,000 deaths
 - *Y. pestis* would remain viable as an aerosol for one hour for a distance of up to 10 km
 - Further spread could occur

Intentional Release of *Y. pestis*

- **Factors influencing size of outbreak:**
 - Quantity of biological agent used
 - Characteristics of the strain
 - Environmental conditions
 - Methods of aerosolization
- **Indications of artificial dissemination:**
 - Occurrence of disease in areas with no enzootic foci
 - Occurrence in persons with no known risk factors
 - Absence of prior rodent deaths



Working Group on Civilian Biodefense

- Series of articles in JAMA
“Medical and Public Health Management Following the Use of a Biological Weapon: Consensus Statements of the Working Group on Civilian Biodefense”
- Representatives from academic medical centers, research, government, military, public health, and emergency management institutions and agencies
- Critical biological agents

Inglesby et al. Plague as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. JAMA. 2000.

Plague as a Biological Weapon – Clinical Manifestations

- Primary pneumonic plague
- Incubation period: 2-4 days (range 1-6)
- First signs of illness
 - Fever with cough and dyspnea
 - Bloody, watery, or purulent sputum
 - Gastrointestinal symptoms may be present



Specimen cup containing purulent, bloody sputum from a pneumonic plague patient, Uganda.

Plague as a Biological Weapon – Clinical Manifestations

- Absence of buboes (except, rarely, cervical buboes)
- Pulmonary disease with areas of profound lobular exudation & bacillary aggregation
- Consolidation on CXR
- **Treat suspect plague patients without waiting for lab confirmation**
- Without treatment, death quickly follows onset of symptoms



CXR of patient with primary pneumonic plague shows extensive lobar consolidation in left lower and left middle lung fields

Treatment of Pneumonic Plague in the Contained Casualty Setting

Preferred Choices

- Gentamicin, 5mg/kg IM or IV once daily or 2mg/kg loading dose followed by 1.7 mg/kg IM or IV 3 times daily
- Streptomycin, 1 g IM twice daily

Alternative Choices

- Doxycycline, 100 mg IV twice daily or 200 mg IV once daily
- Ciprofloxacin, 400 mg IV twice daily
- Chloramphenicol, 25 mg/kg IV 4 times daily

Adults

For children – same antibiotics but different dosing

Treatment of Pneumonic Plague in the Contained Casualty Setting

Pregnant
Women

Preferred Choice

- Gentamicin, 5mg/kg IM or IV once daily or 2mg/kg loading dose followed by 1.7 mg/kg IM or IV 3 times daily

Alternative Choices

- Doxycycline, 100 mg IV twice daily or 200 mg IV once daily
- Ciprofloxacin, 400 mg IV twice daily

Treatment of Pneumonic Plague in the Mass Casualty Setting and for Postexposure Prophylaxis

Adults
(including
pregnant
women)

Preferred Choices

- Doxycycline, 100 mg orally twice daily
- Ciprofloxacin, 500 mg orally twice daily

Alternative Choice

- Chloramphenicol, 25 mg/kg orally 4 times daily

For children – same antibiotics but different dosing

Infection Control Measures for Pneumonic Plague Patients

- **Respiratory droplet precautions** until at least 48 hours of antibiotic therapy and clinical improvement is seen
 - Disposable surgical masks
 - Gown, gloves, and eye protection
- Bodies of patients who have died should be handled with strict precautions
 - Aerosol-generating procedures during autopsy not recommended



Environmental Decontamination Recommendations for Plague

- Plague bacilli are sensitive to sunlight and heating
 - No spore form in *Y. pestis* life cycle
 - Does not survive long outside the host
- No evidence that plague bacilli pose an environmental threat following dissolution of primary aerosol
- Standard precautions for cleaning patient rooms and linens



TULAREMIA: GENERAL INFORMATION

Tularemia - Overview



- Caused by *Francisella tularensis* – small, nonmotile, aerobic, gram-negative coccobacillus
- Hardy – survives well in water, moist soil, straw, decaying animal carcasses
- First identified in 1911 as plague-like illness of ground squirrels in Tulare County, CA
- Aka “rabbit fever”

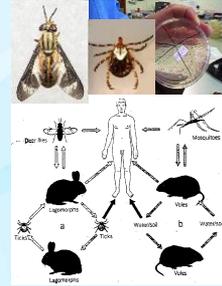
Francisella basics

- *Francisella tularensis* recovered from >200 animal species, soil, water
 - *F. tularensis* subsp. *tularensis* (type A)
 - *F. tularensis* subsp. *holarctica* (type B)
- Genus also comprised of other organisms widespread in environment, including:
 - *F. novicida*, *F. philomiragia* (brackish or salt water)
 - *F. noatunensis*, *F. haliotida*, *F. piscicida* (fish/mollusks)
 - Several other species not fully characterized

Transmission

Multiple modes of infection

- Arthropod bites (ticks, deerflies)
- Handling infected tissues or fluids
- Ingestion of contaminated water
- Inhalation of infective aerosols (agricultural dusts, laboratory)



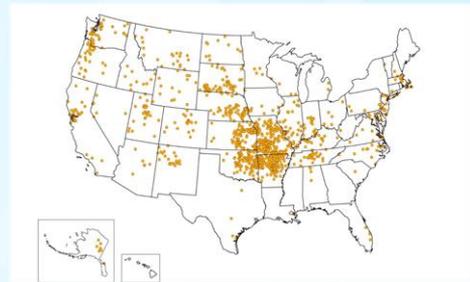
Person-to-person transmission not documented

Tularemia

"I know of no other infection of animals communicable to man that can be acquired from sources so numerous and so diverse. In short, one can but feel the status of tularemia, both as a disease in nature and of man, is one of potentiality."

R.R. Parker (1934)

Geographic Distribution of Reported Tularemia Cases, United States, 2004-2013



Tularemia cases by month – United States, 2001-2010



Clinical Presentation

Symptoms & severity vary based on route of infection

- **Ulceroglandular** – cutaneous ulcer/papule & regional lymphadenopathy
- **Glandular** – regional lymphadenopathy
- **Oculoglandular** – conjunctivitis & regional lymphadenopathy
- **Oropharyngeal** – pharyngitis/tonsillitis
- **Typhoidal** – fever without localizing signs
- **Pneumonic** – respiratory disease



Ulceroglandular tularemia



Cervical lymphadenitis

Intentional Release of *F. tularensis*

- Bioterrorist attack would most likely occur via aerosolization of *F. tularensis*
- 1970 WHO expert committee report
 - 50 kg of virulent *F. tularensis* released as aerosol
 - Metropolitan area of 5 million
- Outcomes
 - 250,000 incapacitating casualties
 - 100,000 deaths
 - Illness expected to persist for several weeks

BioWatch

- Federal government program to detect the release of pathogens into the air as part of a terrorist attack on major American cities
- Created in 2001 in response to anthrax attacks
- System of filters located within existing Environmental Protection Agency air filters that monitor air quality.
- Cross-reactivity with naturally-occurring *Francisella* spp.
- CDC provides SME support on national calls and on-site investigations

Inhalational Tularemia

- Incubation: 3-6 days for acute symptoms (range 1-14 days)
 - Only 25-50% of patients may have radiologic evidence of pneumonia in early stages of infection
- Acute illness with one or more of the following signs/symptoms:
 - Pharyngitis
 - Pleuropneumonitis
 - Manifestations of systemic illness
 - Bronchiolitis
 - Hilar lymphadenitis
- Inhalational exposures can present as systemic illness with few signs of respiratory disease

Inhalational Tularemia - Continued

- Earliest radiographic findings may be:
 - Peribronchial infiltrates – typically advancing to broncho-pneumonia in one or more lobes
 - Accompanied by pleural effusions and hilar lymphadenopathy
- However, signs may be minimal or absent
 - Some patients show only one or several small, discrete pulmonary infiltrates, or
 - Scattered granulomatous lesions of parenchyma or pleura



CXR showing bilateral pneumonitis and left pleural effusion

Epidemiology of Tularemia Following Intentional Release

- First indication of clandestine release
 - Cluster of acute, severe respiratory illness with unusual epidemiologic features
- Early diagnosis of inhalation tularemia requires a high index of suspicion
- Unlikely that serendipitous lab identification would be sentinel event
 - Identification of *F. tularensis* in clinical specimens may be missed or delayed for days when routine screening procedures for bacterial pathogens are followed

Dispersal after Intentional Release

- Under natural conditions, *F. tularensis* can survive for extended periods in cold, moist environment
- Survival of intentionally dispersed particles is unknown but expected to be limited
 - Expect a short half-life due to desiccation, solar radiation, oxidation, and other environmental factors
 - Very limited risk from secondary dispersal

Treatment of Tularemia in the Contained Casualty Setting

Adults

Preferred Choices

- Streptomycin, 1 g IM twice daily
- Gentamicin, 5mg/kg IM or IV once daily

Alternative Choices

- Doxycycline, 100 mg IV twice daily
- Chloramphenicol, 15 mg/kg IV 4 times daily
- Ciprofloxacin, 400 mg IV twice daily

For children – same antibiotics but different dosing

Treatment of Tularemia in the Contained Casualty Setting

Pregnant Women

Preferred Choices

- Gentamicin, 5mg/kg IM or IV once daily
- Streptomycin, 1 g IM twice daily

Alternative Choices

- Doxycycline, 100 mg IV twice daily
- Ciprofloxacin, 400 mg IV twice daily

Treatment of Tularemia in the Mass Casualty Setting and for Postexposure Prophylaxis

Adults (including pregnant women)

Preferred Choices

- Doxycycline, 100 mg orally twice daily
- Ciprofloxacin, 500 mg orally twice daily

Children

Preferred Choices

- Doxycycline
 - If \geq 45 kg, give adult dose
 - If $<$ 45 kg, give 2.2 mg/kg orally twice daily
- Ciprofloxacin, 15 mg/kg orally twice daily

Infection Control Measures for Inhalational Tularemia Patients

- No human-to-human transmission of tularemia documented
- Standard precautions are appropriate
- Isolation of patients is not recommended
- Bodies of patients should be handled using standard precautions
 - Autopsy procedures likely to produce aerosols should be avoided
- **Caution for laboratory workers**

IN SUMMARY...

Differential Diagnosis: Inhalational Tularemia, Plague and Anthrax

- Plague: progress rapidly to severe pneumonia
 - Copious watery or purulent sputum production
 - Hemoptysis, respiratory insufficiency, sepsis and shock
- Tularemia: slower progression of illness and lower case fatality rate
- Anthrax: characteristic findings of prominent mediastinitis
 - Absence of bronchopneumonia
 - Develop fulminating, toxic, fatal illness despite antibiotic treatment

CDC RESOURCES & ACTIVITIES

CDC Resources & Activities

- Track and report on national epidemiology
- Subject matter expertise for health departments and clinicians
- Health communications assistance
- Ecologic and entomologic guidance
- Outbreak response
e.g. Devils Tower, Wyoming

CDC Laboratory Resources & Activities

- WHO Collaborating Center on Vector-Borne Bacterial Diseases
- National strain reference collections
2,500 *Yp* + 1,200 *Ft* strains
- Reference diagnostic services and training
 - Molecular characterization and antimicrobial susceptibility testing
 - Laboratory Response Network coordination and reagent distribution
- R&D for new diagnostics



Questions?

Thank you!

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