Vector-Borne and Rodent-Associated Disease Organisms as Agents of Bioterrorism

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Class A Bioterrorism Agents/Diseases
- Definition -
Includes those organisms that:
• Are easily disseminated or transmitted from person to person
• Can result in high mortality rates and have the potential for major public health impact
• Can cause public panic and social disruption
• Require special action for public health preparedness

Class A Bioterrorism Agents/Diseases
• Anthrax (*Bacillus anthracis*)
• Plague (*Yersinia pestis*)
• Smallpox (variola major)
• Botulism (*Clostridium botulinum* toxin)
• Tularemia (*Francisella tularensis*)
• Viral hemorrhagic fevers (certain filoviruses and arenaviruses)
### Class B Bioterrorism Agents/Diseases

**- Definition -**

Includes organisms that:

- Are moderately easy to disseminate
- Result in moderate morbidity rates and low mortality rates
- Require specific enhancements of CDC’s diagnostic capacity and enhanced disease surveillance

- Brucellosis (*Brucella* species)
- Epsilon toxin of *Clostridium perfringens*
- Food safety threats (e.g., *Salmonella* sp., *E. coli* O157:H7, *Shigella*)
- Glanders (*Burkholderia mallei*)
- Melioids (*Burkholderia pseudomallei*)
- Psittacosis (*Chlamydia psittaci*)
- Q fever (*Coxiella burnetii*)
- Ricin toxin from *Ricinus communis* (castor beans)
- Staphylococcal enterotoxin B
- Typhus fever (*Rickettsia prowazekii*)
- Viral encephalitis (alphaviruses - e.g., VEE, EEE, WEE)
- Water safety threats (e.g., *Vibrio cholerae*, *Cryptosporidium parvum*)

### Class C Bioterrorism Agents/Diseases

**- Definition -**

Includes emerging pathogens that could be engineered for mass dissemination in the future because of:

- Availability
- Ease of production and dissemination
- Potential for high morbidity and mortality rates and major public health impact

Vector-Borne Disease as Bio-Terror Agents
Class C Bioterrorism Agents/Diseases

- Emerging infectious diseases such as Nipah virus and hantavirus
- Hantaviruses and other viruses can be rodent-borne or carried by other small mammals such as bats
- How likely to be used as agents of bioterrorism?

Characteristics of a “Good” Bioterrorism Agent

- Availability (widespread or easy to obtain?)
- Dissemination (mode of spread)
- Production (within terrorists’ capabilities?)
- High mortality and panic
- Escape into nature?

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)
**Francisella tularensis**

- McCoy discovers agent in Tulare County, California during 1911 plague investigation
- Caused plague-like illness in rodents (fever, lymph node swellings, bacteremia, liver and spleen infection, etc.)
- First described by Edward Francis
- Small gram-negative coccobacillus
- Often called rabbit fever or deer fly fever
- Potentially fatal in humans, particularly Type A tularemia infections

**Taxonomy and Geographic Distribution**

- F. t. holarctica (Type B)
- F. t. tularensis (Type A) and F. t. holarctica (Type B)
- F. novicida
- F. t. mediaasiatica

- Gram-negative coccobacillus
- Slow, fastidious growth (cysteine glucose blood agar)
- Lipidated capsule; hardy saprophyte - survives well in water, moist soil, and decaying animal carcasses
- Little is known about virulence factors of F. tularensis
- Two distinct biovars (Type A and Type B) and recently F. t. novicida (formerly F. novicida) – Type A occurs in North America; Type B holarctic; F. novicida questionable as human pathogen; Type A now divided into Type A1 and A2 (A1 most virulent)
- Diagnose by culture (blood or other tissues), serology or FA
- Appears to survive better than plague bacteria when found outside hosts or vectors (especially type B strains)

Vector-Borne Disease as Bio-Terror Agents
**Francisella tularensis**
- Illness in Humans -
  - Plague-like disease
  - Many forms (ulceroglandular, glandular, oculoglandular, septic tularemia, oropharyngeal tularemia, and pneumonic tularemia)
  - 2-5 day incubation period
  - Similar onsets (sudden, fever 100-104°F, chills, headache, generalized aches, cough, chest pain)
  - Lymph nodes often swollen, particularly those near site of inoculation
  - Symptoms can persist for several weeks without treatment
  - Treatable with antibiotics (streptomycin, gentamycin, tetracyclines, chloramphenicol)
  - Mortality without treatment is about 5-10% for Type A infections (Eastern U.S. strains) (40-60% for typhoidal or pneumatic forms), while Type B infections caused lower than 3% mortality.

**Clinical Syndromes of Tularemia**

- **Ulceroglandular tularemia**
  - Cervical lymphadenitis in patient with pharyngeal tularemia
  - Chest radiograph of patient with pulmonary tularemia (Radiograph shows bilateral pneumonitis and left pleural effusion)

**Reservoirs and Vectors of Tularemia**
- Main reservoirs (persons handling these can acquire tularemia)
  - Rodents (voles, muskrats, ground squirrels, beavers)
  - Lagomorpha (hares and rabbits)
  - Probably all mammals can be infected but only the above are likely to be reservoirs
- Vectors
  - Ticks (biological, transstadial, transovarial?) – Dermacentor variabilis, D. andersoni, Amblyomma americanum, Ixodes scapularis (U.S. and elsewhere)
  - Deer flies (mechanical – many questions remain) – Chrysops discalis and other Chrysops spp. (primarily western U.S.)
  - Mosquitoes (mechanical – probably poor vectors) – mainly Aedes (primarily Sweden)
  - Fleas (mechanical – very poor vectors) – multiple genera
Tularemia also can be water-borne
- Outbreaks among beavers and muskrats in U.S.
- Water voles and European beavers in Eurasia
- Crayfish in Spain
- Human water-borne outbreaks in Eurasia and U.S. (contaminated water and muskrat trappers)
- Persistence in amoebae?
- Contaminated hay (Eurasia – vole urine)
- Consumption of contaminated prey or other items
- Airborne infections (pneumonic tularemia) – Martha’s Vineyard (no human to human spread)

Francisella tularensis – U.S. Epidemiology
- 1368 cases reported from 1990-2000
- Four states had 56% of all cases (Arkansas – 23%; Missouri - 19%; South Dakota – 7%; and Oklahoma – 7%)
- Highest incidences among
  - Persons aged 5-9 years and 75 or over
  - Males in all age categories
  - American Indians/Alaska Natives
- Onsets for 76% of cases occurred from May-August
- Reporting decreased in the last half of the 1990s
- Most infected through arthropod bites (mainly ticks), contact with infected animals (mainly rabbits)
- Possible decrease in rabbit hunter cases and increase in those exposed to infectious ticks or flies
- Outbreaks associated with handling muskrats, tick and deerfly bites, lawn mowing or cutting brush. Occasional cases from contaminated water, handling rabbits, etc.
- Laboratory risks are high

Vector-Borne Disease as Bio-Terror Agents
Tularemia Prevention

- Wear protective clothing and repellents (DEET)
- Spray clothes with permethrin
- Examine skin and clothes for ticks
- Avoid contact with sick or dead animals or contaminated water
- Use gloves when cleaning game
- Laboratorians should be vaccinated
- Monitor exposed persons for signs of illness
- Education of public, veterinary staff, health care providers

Tularemia as a BT Agent

- Extremely infectious (< 10 organisms)
- Relative ease of dissemination
- Substantial capacity to cause illness and death
- Reportedly engineered for antibiotic and vaccine resistance
- Possibly used before (WWII?)
- Developed by Soviets in post-WWII years

Tularemia and BT - Airborne Release -

- 3-5 days incubation period
- Develop acute, undifferentiated febrile illness with pneumonia, pleuritis and hilar lymphadenopathy
- Confusion with community-acquired pneumonia?
- Environmental contamination?
- Risk of secondary cases arising from spread to vectors and rodents or lagomorphs?
**Tularemia**

- Non-airborne Releases -
  - Water (epidemics on record – typhoidal or glandular tularemia)
  - Food?
  - Vectors or hosts?

**Tularemia in an Age of Bioterrorism**

- Tularemia detection in air sensors - USA (Texas, Washington, DC false alarms)
- BT event versus environmental background or related Francisella species?

**Environmental Responses to an Intentional Release of Tularemia Bacteria**

- Many similarities with plague responses
- Animal-based surveillance
  - Vector surveillance
  - Veterinary surveillance
  - Rodents, rabbits and other "wild" hosts
- Vector and host control
- Education about ongoing risks and personal protection
- Possible risks with untreated water? Contaminated foods?
Yersinia pestis

- Cause of the Black Death and two other major pandemics
- Gram-negative bacterium
- Highly pathogenic and often fatal
- Multiple modes of spread (flea bite, animal contact, inhalation)
- Maintained in flea-rodent transmission cycles

Yersinia pestis - Modes of Transmission -

- Flea bite
- Direct Contact with infectious tissues or body fluids
- Inhalation of infectious respiratory droplets or other materials

Plague Cycle - Multiple Modes of Spread -

Wild Rodent Cycle

- Direct contact

Domestic Cycle

- Direct contact

Wild Rodent Cycle

- Direct contact

Plague Cycle - Multiple Modes of Spread -

Vector-Borne Disease as Bio-Terror Agents
Plague in the United States

Multiple Modes of Spread

Primary Mode of Transmission

Epizootic Cycle

Enzootic Cycle

"Incidental" Hosts

Flea Transport

Flea Bite or Consumption

Pneumonic Person to Person Transmission

Pneumonic Disease

Plague in the United States

Flea Bite or Consumption

Severity of Illness - Bubonic Plague -

- Incubation: 2-6 days
- Fever, chills, headache, myalgias, prostration, occasionally nausea and diarrhoea
- Swollen lymph nodes or buboes
- 40-60% fatal without treatment (14% of U.S. cases fatal, 1970-present)

Severity of Illness - Pneumonic/Septic Disease -

- Short incubation period (1-4 d)
- Acute, fulminating course
- Physiologic catastrophe (SIRS)
- Intensive medical/nursing support required
  - Isolation, respiratory and other organ support, 2-3 wk hosp, slow convalescence
- Death in 3-6 days if not treated early

Vector-Borne Disease as Bio-Terror Agents
Plague as a BT Agent

- High epidemic potential
- Multiple modes of spread
- Very severe or fatal illness
- Can create panic (cultural)
- High availability
- Potential to form new foci
- Soviets had it in their arsenal and others have used it in the past (Siege of Caffa, Japanese in WWII)
- Can be modified for antibiotic resistance, heightened virulence (e.g. myelin toxin – see Alibek)

Plague’s Ability to Create Panic

- Pandemics
  - Justinian’s Plague
  - Black Death
  - Modern Pandemic, especially in India
- India 1994
- How would the U.S. and other industrialized countries react?
- Even individual cases in U.S. cause considerable local reaction, especially when they cause fatalities or affect children
- A terrorist behind every bush?
- Chicago rat episode

Plague in India – Surat Outbreak

- Indian outbreak was a major surprise – no plague confirmed in India since 1966
- Caused a panic within India and surrounding states
- Caused DG/WHO to invoke article 11 of IHR
- Caused huge economic loss for India (> $3 billion)
False Accusations of BT/BW in India

- Tabloid style “News magazine” accuses U.S. Army of releasing novel plague strain in Surat
- CDC personnel accused of participating in evaluation of the “planned release” by the U.S. Army
- Resulted in diplomatic responses and vehement denials by U.S.
- India has made enormous strides in improving their surveillance, prevention and diagnostic capabilities in the past few years and has responded well to recent plague outbreaks.

Plague as a BT Agent
- Availability Through the Mail
  - Pre-1995 available from many sources, including ATCC
  - Ohio man ordered plague strains from ATCC to do “experiments and vaccine development” in his basement and garage
  - CDC successfully worked with Ohio Dept. Health and local authorities to recover strains
  - Individual used fake letterhead and other misrepresentations to obtain the strains – charged with mail fraud
  - Shipment and transfer of Y. pestis and other select agents now tightly regulated

Can Terrorists Find Sources of Plague Bacteria?
- Problem of Availability in Natural Environments
  - Plague originated in central Asia
  - Spread long ago to east-central Africa
  - Carried around world during last pandemic (1894-1920s)
  - Foci exist in 5 continents and many countries
  - Persons with appropriate microbiological and field investigation skills can obtain isolates relatively easily

Vector-Borne Disease as Bio-Terror Agents
Plague Outbreaks or Isolated Cases During the Past 15 Years (Selected Examples)

- China (rat fleas in SW and marmot hunters in NW)
- Mongolia (marmot hunters)
- Kazakhstan and Jordan (camels)
- Indonesia (rat fleas on volcanoes)
- India (1994 and 2002)
- Vietnam (recent drop in cases?)
- Madagascar (650-2900 cases/year)
- Tanzania, Democratic Republic of Congo, Uganda, Mozambique, Malawi, Zambia, Namibia (recent large outbreaks)
- Algeria (near Oran – reactivation of old focus?)
- Peru, Ecuador and Brazil (guinea pigs and/or wild rodent fleas)
- United States (wild rodent fleas, rodents, cats, and canines)


Spread of Plague in the U.S. following a BT Event

- Would plague spread in non-endemic areas?
- How long would the agent persist in local environments?
- Could it cycle in local host and vectors? (Remember the rapid spread of West Nile Virus)
- "Natural experiment" when plague was introduced in early 1900s along Gulf and Pacific Coasts during the last pandemic
- Failed to persist along the Gulf Coast but spread quickly from Pacific Coast
- Suggests some areas in U.S. are not suitable for plague foci
- Supported by ecological niche modeling (Collaboration with A. Townsend Peterson at KU)

Plague Risks in a BT Event - Airborne Release –

- Greatest BT concern for plague
- 2-3 day incubation; severe pneumonia
- Many “first wave” pneumonic cases
- High fatality rate for pneumonic plague
- “Second wave” of pneumonic cases?
- Spread to local animal populations?

Airborne Plague Release - Unknowns -

- Strains altered for survival?
- Strains altered for antibiotic resistance?
- Rate of secondary spread? (overestimated?)
- Animal/flea involvement - bubonic cases?
- Other ongoing environmental risks (probably low)

Vector-Borne Disease as Bio-Terror Agents
Plague and BT
- Release of infected animals or fleas –
  • Not as likely as airborne release
  • Most cases will be bubonic
  • Depends on X. cheopis infestations on rats
  • Rats in many areas have few fleas
    (So. California suburbs / Dallas 1993)

Identifying a Plague-related BT Event
• Sudden appearance of multiple cases
• Cases in non-endemic areas
• Unusual animal die-offs in non-endemic areas
• Suspicious event or observation
• Y. pestis detected in environmental sampler

Note: Knowledge of naturally occurring plague is important

Identifying a Plague-related BT Event
- Peripatetic Cases -
• New York City (2002) – New Mexico residents who traveled to NYC
Plague Cases in New York City

- 47 y.o. female and 53 y.o. male travel to NYC on 11/1/02
- Became ill on 11/3/02
- Hospitalized on 11/5/02
- Both had swollen inguinal lymph nodes and fever
- Y. pestis isolated from male; serology still pending on female

History:
- Residents of New Mexico
- Plague-positive wood rat fleas at house in July

Peripatetic Case Investigation

- Probable exposure near home
- Positive wood rat fleas identified at site in July
- Couple and neighbors warned about plague
- Case investigation identified positive fleas from Peromyscus and Neotoma
- Molecular typing studies indicated that patient isolate was close to flea isolates

BT Responses for Plague and Tularemia

- Much learned over last century
  - Etiologic agents
  - Course of illnesses
  - Modes of spread
  - Treatment of cases
  - Control (airborne, vectors and hosts)
- Use past knowledge for planning
- Remain flexible (altered strains, etc.)
Plague and Tularemia Bioterrorism Response

Responders:
• State and local governments
• DVBID and other CDC personnel
• Other federal agencies (CCRF, NIH, and others)
• DOD
• Academia

Response Plans:
• Epidemiologic responses
• Diagnostics
• Environmental evaluations
• Vector and rodent control

Response Teams
• Command and support Team
• Animal and vector surveillance teams
• Animal necropsy and processing teams
• Vector and host control teams
• Veterinary surveillance team
• Lab support team (onsite)

Animal-Based Surveillance Plan
• Provide information on environmental risks
• Determine whether plague or tularemia is spreading in animal and vector populations
• Assess need for vector and host control
• Recommend and implement appropriate control and prevention measures
• Develop appropriate follow-up surveillance procedures
Conclusions

• Threat of terrorists using vector-borne agents should be taken seriously
• Many unknown factors, including
  – Modes and sites of release
  – Rates of spread
  – Populations targeted
  – Possible genetic modifications to the agents (antibiotic resistance, virulence factors, etc.)
  – Whether agent will persist and spread in environment (likely for vector-borne agents?)
• Best defense is
  – continuing vigilance
  – strong intelligence and investigative capabilities
  – adequate public health preparation
  – training of key personnel
  – development of response plans
  – effective coordination between responders (CDC, state, local, other federal, DOD, and academia)

Vector-Borne Disease as Bio-Terror Agents