Overview

- Focus will be on biologic agents
- Discuss available prophylaxis & therapeutic measures
- Look at our state of preparedness on a local, state, & national level
- Consider measures for your own personal safety & that of your family

Terrorism (Code of Federal Regulations)
- The unlawful use of force and violence against persons or property to intimidate or coerce a government, the civilian population, or any segment thereof, in furtherance of political or social objectives

Bioterrorism
- Use of biological agents to intentionally produce disease or intoxication in susceptible populations to meet terrorist's aims.
- First act of U.S. Biowarfare 1763
  - Sir Jeffrey Amherst ordered British troops to give blankets infected with smallpox to Indian tribes

3 Critical Elements for Bioterrorism

- Perpetrators
  - State sponsored
  - Insurgent rebels
  - Doomsday/cult-type groups
  - Nonaligned terrorists
  - Splinter groups
  - Lone offenders

- Biologic Agent
  - >12 nations either have or are pursuing programs to develop biologic weapons
  - Reported loss of biologic agents from former Soviet Union
  - Technical means to disseminate agent

Logistics for Biologic Attack

- Variable access to biologic agents
  - Up until recently B. anthracis could be obtained from reference collections
  - Requires some technical know how and equipment but nothing out of the ordinary

- Methods to disperse agents generally available
  - Commercial products available that disperse small particles (<10 microns)

- Surprise, likely a silent attack requiring several days before being detected
  - Expect unusual means of deployment
Biologic Agent Properties

- High infectivity
  - Small dose required to produce disease
  - Spread person to person for secondary effect
- Either fatal or highly incapacitating
- Can be dispersed and stable to environment once released
- No effective prophylactic or treatment measures
  - Potentially could genetically alter agent for this effect

Soviet Program

- Between 1972 & 1992 Soviet launched a full scale effort to generate biologic weapons
  - Biopreparat guise was as a pharmaceutical company
  - ~40 different facilities
  - At maximum could produce 2 tons of anthrax spores per day
- At the program’s peak > 30,000 people worked full time on this program
- Parts of program re-enacted in Iran, Iraq, & North Korea

Category A Agents

- Agents that can:
  - Easily disseminated or transmitted from person to person
  - Causes high mortality & potential for major public health impact
  - Could cause panic and social disruption
  - Requires special action for public health preparedness

Class A Agents

- Variola major (Smallpox)
- Bacillus anthracis (Anthrax)
- Yersina pestis (Plague)
- Clostridium botulinum toxin (Botulism)
- Francisella tularensis (Tularemia)
- Filoviruses
  - Ebola (Ebola hemorrhagic fever)
  - Marburg (Marburg hemorrhagic fever)
- Arenaviruses
  - Lassa (Lassa fever)
  - Junin (Argentine hemorrhagic fever)

Category B Agents

- Agents that can:
  - Moderately easy to disseminate
  - Causes moderate morbidity & low mortality
  - Requires special enhancements of CDC’s diagnostic capacity and disease surveillance

Class B Agents

- Coxiella burnetii (Q Fever)
- Brucella spp. (Brucellosis)
- Burkholderia mallei (Glanders)
- Alphaviruses
  - Venezuelan encephalomyelitis
  - Eastern & Western encephalomyelitis
- Ricin toxin (castor beans)
- Epsilon toxin from Clostridium perfringes
- Staphylococcus enterotoxin B
Class B Agents Spread by Food and Water
- Salmonella spp.
- Shigella dysenteriae
- E. coli (O157:H7)
- Vibrio cholerae
- Cryptosporidium parvum

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Category C Agents
- Agents:
  - Availability
  - Ease of production and dissemination
  - Potential for high morbidity and mortality and major health impact

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Class C Agents
- Nipah virus
- Hantaviruses
- Tickborne hemorrhagic fever viruses
- Tickborne encephalitis viruses
- Yellow fever
- Multidrug-resistant tuberculosis

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Anthrax: Historical Perspective
- Cited in the book of Genesis
  - Referred to as the 5th plague in 1491 BC
  - Described as “killing the Egyptian’s cattle”
- 17th Century, “Black Bane” swept through Europe causing animal & human death
- Normally, disease of grazing animals
  - Anthrax spores found in soil
- Occupational outbreaks described in the 1800’s
  - Wool sorter’s disease

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Anthrax (Bacillus anthracis)
- Most countries attempting a biologic weapons program had or have anthrax
- To weaponize, product must be milled (1-5 micron size) & overcome electrostatic forces
  - Microencapsulation or surfactants
  - “Infective dose” data likely inaccurate with new forms
- Pathogen attacks monocyte
  - Protective antigen with lethal factor & edema factor
  - Toxin causes release of IL-1beta & TNF-alpha

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Anthrax (Bacillus anthracis)
- Routes of transmission: skin, GI tract, and inhalation of spores
  - Not spread person to person
- Most cases will occur in first two weeks of exposure but additional cases will present over next month (Sverdlovsk, USSR)
- Initial symptoms that of a cold or flu then abruptly turn to respiratory distress
  - Dyspnea and chest discomfort common
  - Rhinorrhea uncommon
- Untreated disease is ~90% fatal
  - Mediastinal widening & meningitis ~50%
  - High probability of bacteremia

Situation Following Dissemination of Spores in U.S. Mail
MMWR 50(Dec 7): 1077-1079, 2001
- 22 Anthrax clinical case exposures
  - 11 Inhalational cases
    - Robert Stevens, 63, photo editor, the Sun, American Media Inc., Boca Raton, Fla. Died Oct. 5.
    - Kathy T. Nguyen, 61, New York City hospital worker. Died Oct 31
    - 94 yr woman resident Oxford, CT Died November 21
  - 11 Cutaneous cases
    - 7 Confirmed
    - 4 Suspected

Shopping Mall Scenario
Osterholm, M.
- Anthrax spores aerosolized into ventilation system
  - Of 10,000 people present 9,000 exposed
  - Attack announced 24 hours later
- 90% of those exposed are started on antibiotic by the end of day 2
- 4950 hospitalized
  - 2925 require ICU
    - 2801 require ventilator
  - 855 deaths

Anthrax
- During a shift change at a plant in Russia milling anthrax spores, a filter was temporarily removed allowing release of spores into air
- Release focused on narrow band of 4km downwind
- 77 cases & 66 deaths
- Livestock killed up to 50 km

Outline of Washington, DC
Office of Technology Assessment 1993

Attack on Major U.S. City Using Aerosolized Anthrax Spores
- 3 Scenarios
  - Clear Calm Night = 300 km² Area
    - No Wind
    - Deaths 1-3 Million
  - Overcast Day or Night = 140 km² Area
    - Moderate Wind
    - Deaths 420,000-1.4M
  - Clear Sunny Day = 46 km² Area
    - Light Breeze
    - Deaths 130,000-400,000

Inhalation Anthrax
Mediastinal widening with inhalation anthrax
JAMA 1999:281:1735-1745
Anthrax Adjunct Therapy

- Newer fluoroquinolones
  - Not all FDA approved but likely effective:
    - Anthrax
    - Plague
    - Tularemia
    - Brucellosis
  - Offers advantage as once a day therapy
    - In emergency can treat twice the number of patients for same volume of drug
- Efforts also directed at blocking anthrax toxin virulence
  - Toxin made of three proteins, 1st attaches to cell & injects the 2 other proteins
  - Have identified cell receptor for toxin & structure of lethal factor

Plague (Yersina pestis)

- Acute febrile lymphadenitis or bubonic plague
  - Result of infected flea bites, rodents serve as flea reservoir
    - Generally 2-8 day incubation period following flea bite
    - Bacteria move via cutaneous lymphatics to regional lymph node
    - Y. pestis phagocytized by PMN’s where bacteria multiply
  - Sudden onset of fever, headache, chills, & weakness
    - Within 24 hours classic genital, axilla, or neck bubo (Do not IND bubo-very infectious)
    - Can have pustules, vesicles, eschar, or papular lesions
    - Purpura can progress to necrosis and distal gangrene
      - Called the Black Death

Plague (Y. pestis)

- Estimates to have killed ~25% of Europe’s population
- Septicemia, pneumonic, or meningeal forms
  - Cultures of blood, sputum, bubo, CSF likely to be positive
- Pneumonic form(Most likely form for terrorists)
  - Patients present with fever, lymphadenopathy, chest pain, hemoptysis
  - Pneumonic form can be spread person to person
  - CXR consistent with bronchopneumonia, confluent consolidation, & cavities may be present
  - Untreated mortality >50%

Tularemia (Francisella tularensis)

- Named for work done by Dr Edward Francis & for work in Tulare County (CA)
- Rabbit or Deerfly fever / Marketmen or Obara’s Disease
- Primarily occurs between 30 & 71 degrees latitude
- Most common between June-August & again in December (bug & hunting season)
- 6 classic forms (ulceroglandular, glandular, oculoglandular, pharyngeal, typhoidal, & pneumonic)
- Symptoms: fever, chills, headache, malaise, anorexia, & fatigue. Cough, myalgia, emesis, pharyngitis, & diarrhea

Tularemia (F. tularensis)

- Continued
  - Fever (>101 F) typically for few days, then abates, then fever & symptoms return
  - Spread by bite of blood feeding insect, contact with contaminated animal products, aerosolized droplets, contaminated water, or animal bites
  - No human to human transmission
  - 3-5 days after bug bite get local papule which over next few days ulcerates, organism spreads via lymphatics, affected tissue will show focal necrosis and may caseate
Smallpox

- Variola major (Orthopox virus)
  - No animal or environmental reservoir
- Very stable in variety of climates
- Some seasonal variation
  - Winter & early spring
- Small infectious dose
  - 1 to 2 virions
  - Likely 4 to > 10 secondary cases per index case
- Last U.S. case 1949

Clinical Course for Smallpox

- Inhale infected droplet or contact with infected material
- Day 1-5 virus spreads lungs to lymph nodes
- Day 6-17 virus moves to liver & spleen to replicate
  - Patient without symptoms & not contagious
- Day 18-20 Fever, fatigue, emesis, sores in mouth & throat
  - Patient now highly contagious
  - Must be within 6 feet for prolonged period
  - Not as contagious as measles, chickenpox, or flu
- Day 21-37 Small bumps noticed, beginning of fluid filled pustules which will scab and fall off
  - Patient contagious until scabs fall off
  - Likely stage of patient’s death

Smallpox Meschede Hospital 1970

- Patient admitted with smallpox (6 day hospital stay)
- Placed in respiratory isolation, hospital was under isolation precautions for flu
- Responsible for 17 cases over following two weeks and 2 additional cases later
  - One case, patient just stayed a few minutes
- Cases occurred throughout hospital & despite patients & healthcare workers all likely being vaccinated

Contraindications to vaccination

- Pregnancy
- Breast Feeding
- HIV
- Eczema
- Organ transplant patients
- Chemotherapy or other forms of immune suppression
- Vaccination of 1 million persons
  - A clinic over two 8 hour shifts inoculate 5,900
  - 20 clinics per state
  - Vaccination requires 15 needle pricks
  - 39 Severe eczema reactions
  - 12 Encephalitis
  - 1 Death

Smallpox Vaccination & ADR’s

- Civilian vaccination program
  - Jan 24th through Feb 28th 12,690 civilians immunized
  - No life threatening events
    - Eczema vaccinatum, SJS, Fetal vaccinia, encephalitis, Progressive vaccinia
  - 2 moderate to severe events
    - Generalized vaccinia, Ocular vaccinia, Pyogenic infection at site
  - 4 serious & 46 nonserious adverse events
    - Fever (2), rash (2), malaise (2), pruritis (2), hypertension (2), pharyngitis (2)
Department of Defense Armed Forces
Epidemiology Board Recommendations for Prophylaxis

- **Anthrax** (*B. anthracis*)
  - Ciprofloxacin (Post Exposure & Treatment)
  - Doxycycline

- **Tularemia** (*Francisella tularensis*)
  - Ciprofloxacin
  - Doxycycline
  - Gentamicin (Treatment)

- **Plague** (*Yersina pestis*)
  - Ciprofloxacin
  - Doxycycline
  - Gentamicin (Treatment)

- **Q Fever** (*Coxiella burnetti*)
  - Doxycycline (Post Exposure & Treatment)

- **Glanders** (*Burkholderia mallei*)
  - Doxycycline

- **Brucellosis** (*Brucella spp.*)
  - Doxycycline

Bioterrorism Summary

- Virtually no U.S. trained physician has seen a clinical case of smallpox, anthrax, plague, etc.

- In initial stages symptoms of biological agents infection are fairly nonspecific
  - Difficult to identify & determine timing of attack

- Clustering of cases may be the clue
  - Syndromic surveillance of ED’s
  - Work attendance & demand for OTC medications

- Need to identify pathogen and if bacterial pathogen, do antibiotic susceptibilities
- Response plans are improving
  - 7000 emergency personnel ready to go
  - Metropolitan Medical Response Plans
  - Would still expect significant public panic

- Morbidity and mortality would be significant for persons initially exposed

Bioterrorism Summary

“...it’s not a matter of if, but when, which agent, & how bad will it be.” M. Osterholm

- Incredibly complicated situation, likely to worsen over time
  - Everyone has been drafted for this war
  - Glass half empty vs half full syndrome

- Solutions to bioterrorism will likely begin to unfold, vaccination programs will grow

- At the present time, we are closing the gap on being prepared for a biological attack
  - Planning & Logistics
  - Supplies, Vaccines, & Medications
  - Personnel