42nd Interscience Conference on Antimicrobial Agents and Chemotherapy

Convener: Nancy Khardori, M.D.

Faculty

Nancy Khardori, M.D., Ph.D. – *Overview, Anthrax*

David Carpenter, Ph.D. – *Laboratory Diagnosis of Biological Weapons*

Subhash Chaudhary, M.D. – *Biological Terrorism – Care of Children*

Janak Koirala, M.D., M.P.H – *Botulism and Tularemia*

James Goodrich, Ph.D., M.D. – *Small Pox, Viral Hemorrhagic Fevers*

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

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OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Biological Warfare Agents

Agents of Biological Terrorism

Biothreat Agents

Critical Biological Agents

Bioweapons – Bioterrorism

Antibioterrorism Measures

Biodefense - Biosafety

Biocrimes

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

"Infectious Disease is one of the few genuine adventures left in the world."

"Infectious Disease is one of the great tragedies of living things - the struggle for existence between different forms of life . . Incessantly the pitiless war goes on, without quarter or armistice - a nationalism of species against species."

Hans Zinsser- Rats, Lice and History (1934)

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

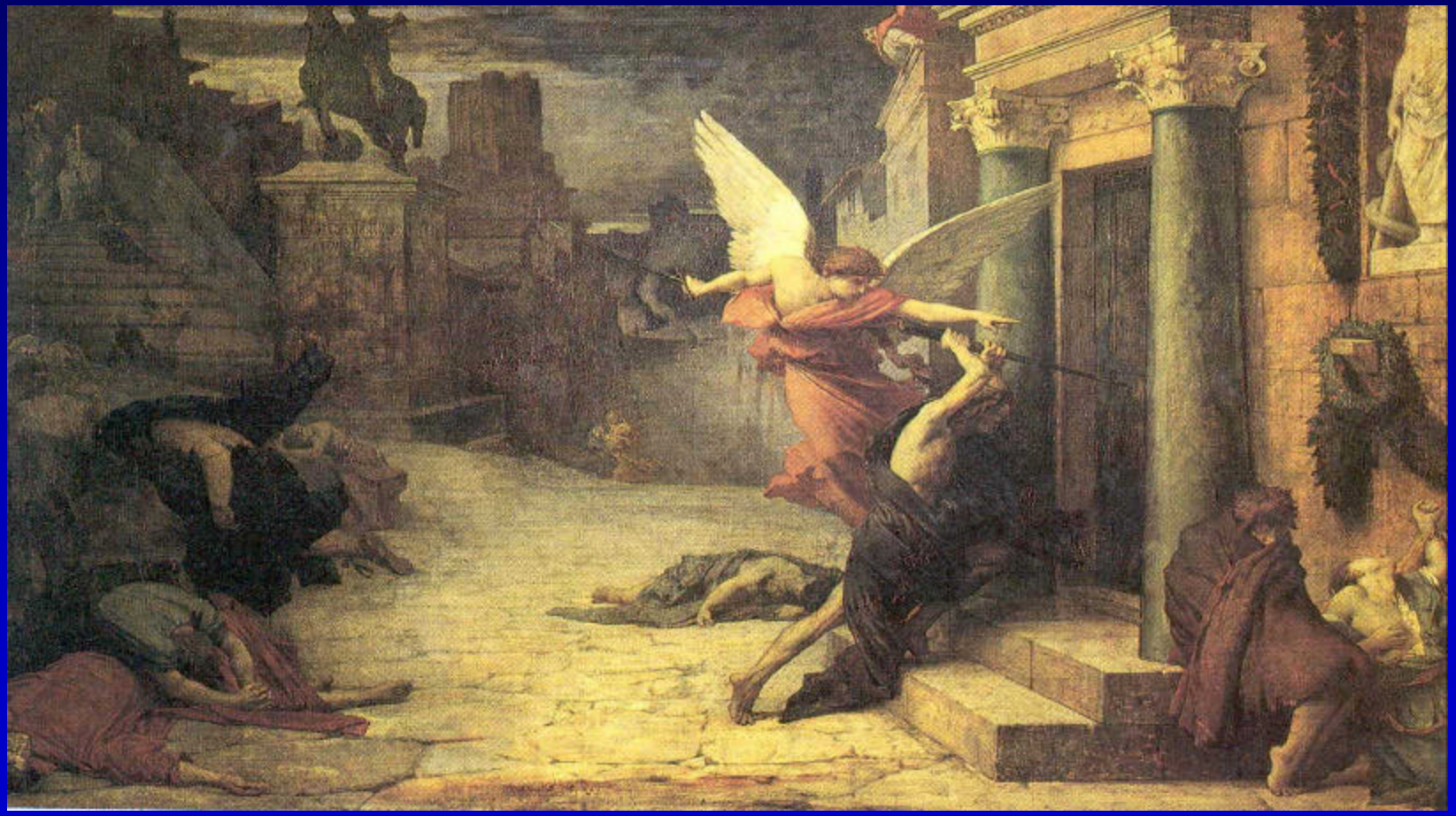
Infectious Agents as Tools of Mass Casualties

- Bubonic plague killed a quarter (approx. 25 million) of the European population in the 14th century)
- Small pox, measles, plague, typhus and influenza

  Estimated to kill 95% of pre-Colombian native American populations.

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Infectious Agents as Tools of Mass Casualties



OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

IAATOMC

Influenza Pandemic killed 21 million people between 1918 - 1919

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

IAATOMC

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

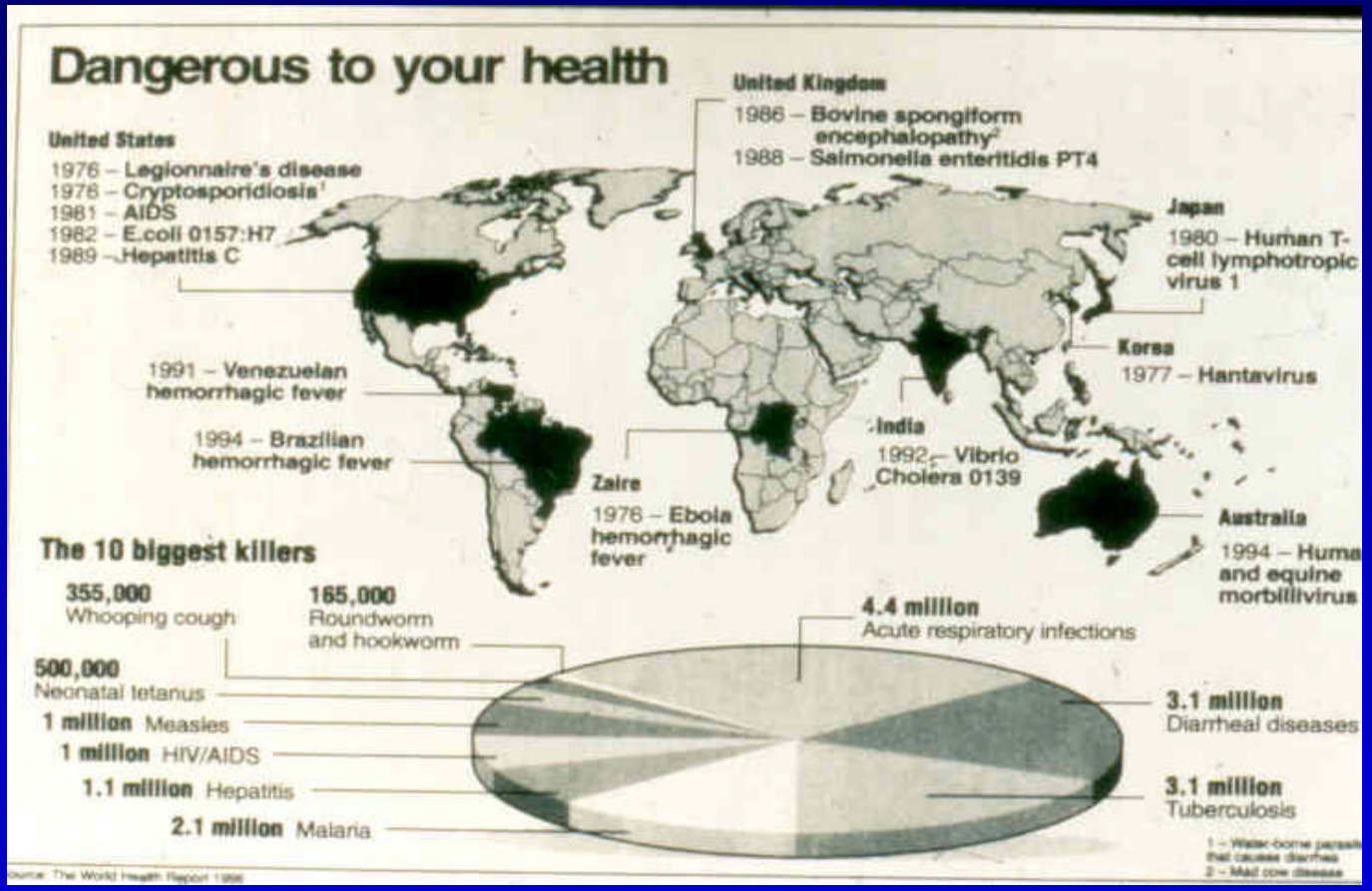
IAATOMC

In the US, approximately 170,000 people die from infectious diseases each year

Worldwide Infectious Diseases remain the major causes of death

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

IAATOMC



OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

IAATOMC

- Global nature and impact of Infectious Diseases threats
- ”The threat of bioterrorism and the spread of Infectious Diseases”

  US Senate Committee on Foreign Relations

  Heyman, WHO, September 5, 2001

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Definition

Bioterrorism “The intentional release of viruses, bacteria or toxins for the purpose of harming and killing civilians.”

CDC July, 2001

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Bioterrorism, National Security, and Law

Bioterrorism - “The intentional use of a pathogen or biological product to cause harm to a human, animal, plant or other living organism to influence the conduct of government or to intimidate or coerce a civilian population.”

Gostin et al, JAMA, August 7, 2002

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Bioterrorism, National Security, and Law

- The Model State Emergency Health Powers Act (MSEHPA)

  JAMA, August 7, 2002

- Bioterrorism, Public Health and Civil Liberties

  NEJM April 25, 2002

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Bioterrorism, National Security, and Law

- Public Health Security and Bioterrorism Preparedness and Response Act of 2002
- Public Law 107 - 188, June 12, 2002
- Title II - To balance Public Health concerns over safety and security with need to protect legitimate scientific research and diagnostic testing

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Bioterrorism, National Security, and Law

- New provisions for the possession, use and transfer of select agents
- Responsible Facility Official (RFO) - Reporting

  CDC and ASM, May - August, 2002

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Bioterrorism, National Security, and Law

- Disease Reporting Laws
- CDC Commission

Journal of Law, Medicine and ethics,

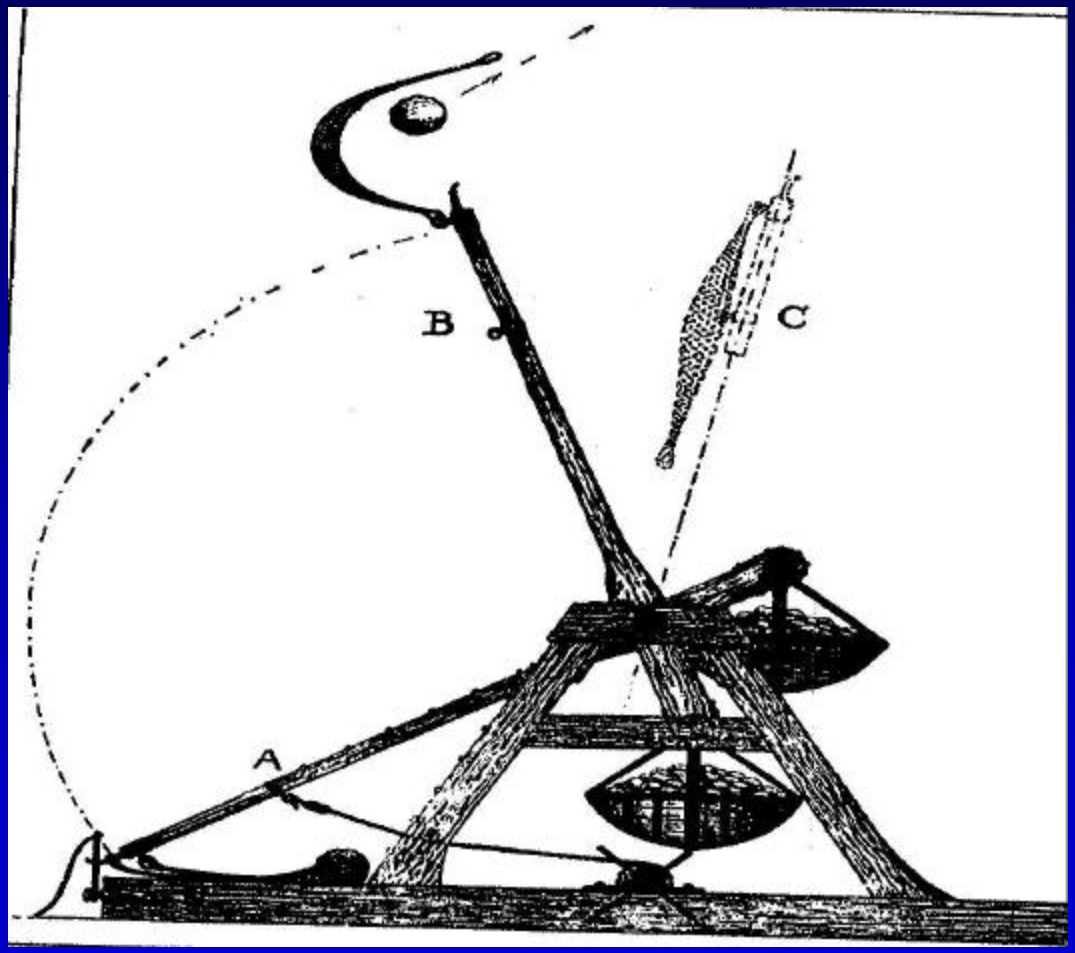
30:262-266, 2002

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Historical Perspective and Trends Related to Bioterrorism

- One of the first recorded events - 184 BC
- Carthaginian soldiers used snakes against King Eumenes
- Catapults - Plague infected bodies into Kaffa - 1346
- Diseased human and animal corpses

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM



OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Historical Perspective and Trends Related to Bioterrorism

1763 —— British Forces – Small pox

1877 —— Koch's Postulates

1910's —— Germany-Anthrax and Glanders

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Historical Perspective and Trends Related to Bioterrorism

1930's, 1940's — Japanese - Plague

1970 — Weather Underground - ??

1972 — R.I.S.E. - Typhoid, Diphtheria, dysentery, meningitis

1978 — Bulgarian defector - Ricin

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Historical Perspective and Trends Related to Bioterrorism

- 1979 — Accidental release - Anthrax, USSR
- 1980 — Red Army – Botulism ??
- 1984 — Rajneeshees - Salmonella
- 1991 — Minnesota Patriots Council - Ricin

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Historical Perspective and Trends Related to Bioterrorism

1995 — Aum Shinrikyo - Anthrax, botulism, Q fever, Ebola

1996 — Laboratory Workers - Shigella

1998 — L.W. Harris - Anthrax

2001 — US Postal System - Anthrax

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Historical Perspective and Trends Related to Bioterrorism

The snakes to catapults to fleas

To

capsomers

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Chronology of Antibioterrorism (Biosafety) Actions

- The Geneva Protocol - 1925
- The Biological and Toxin Weapons Convention - (BWC) 1972*
- The Chemical Weapons Convention - 1997
- The Draft Protocol to Strengthen the BWC - July, 2001
- The Fifth BWC Review Conference - November, 2001

*143 states and 18 signatories

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

The US Program

Offensive Biological Program – 1942

The War Reserve Service

Expanded During Korean War – 1950 – 1952

Simulants released in New York City, San Francisco etc. 1949 – 1968

Nosocomial epidemic – 1950 – 1951 of *S. marcescens* UTI

Termination of Program – 1969 – 1970

Defensive Program Against Biological Weapons - 1953

USAMRIID – Ft. Detrick, Maryland

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

The US Program – Agents Used

Weaponized

Lethal Agents	Incapacitating Agents
Bacillus anthracis	*Brucella suis*
Botulinum toxin	*Coxiella burnetii*
Francisella tularensis	Staphylococcus Enterotoxin B
	Venezuelan equine - Encephalitis virus

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

The US Program – Agents Used

Stockpiled but not Weaponized

Anticrop Agents

Rice blast

Rye stem rust

Wheat stem rust

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Repositories and Sources (Pre BWC)

- Soviet Union Experimental Work - 1920's
- Post War Military Building programs
  - The Soviet Union
  - The Allied Biological Weapons Program

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Repositories and Sources (Post BWC)

- Biopreparat - Soviet Politburo - 1973 - 1974
- Iraq's Biological Weapons Program - 1974
- Vector in Kottsovo, Novosibirsk - visited 1997
- Obolensk in Moscow, visited 2000
- Estimated 10 (possibly 17) nations possess BWAs

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Repositories and Sources (Post BWC)

- Well financed organizations - Aum Shinrikyo
- Smaller less sophisticated organizations - Rajneeshees
- Smaller groups – R.I.S.E. Weather Underground
- Individuals - Larry Wayne Harris

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

The Threat

Biological Weapons System

- Payload - The agent itself
- Munition - Protects and maintains potency
- Delivery System
  - Missiles
  - Vehicles
  - Artillery Shells
- Dispersion System
  - Aerosol sprays
  - Explosives
  - Food and Water

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

The "Favorable" Characteristics

- 600 to 2000 times cheaper than other weapons of mass destruction
- 0.05% the cost of a conventional weapon to produce similar number of mass casualties per square kilometers
- Technology common and easy
- Delivery systems easily available

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

The "Favorable" Characteristics

- Aerosols - The most effective means of dispersion
- Invisible, silent, odorless, tasteless

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

The "Favorable" Characteristics

- Incubation period - the natural lead time
- Confusion between sporadic/endemic disease and bioterrorism
- Secondary or tertiary transmission person to person and vectors

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Consequences of Biological Weapons' Use

- Mass effect - 1 kg anthrax can kill 100,000 people
- Overwhelmed services and health care system
- Delayed diagnosis - unfamiliarity
- High morbidity and mortality
- Economic impact (26.2 billion/100,000 persons exposed to anthrax)
- Psychological impact
- Long term effects

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Types of Bioterrorism Attacks

- Overt versus covert (more likely)
- Announced versus unannounced (more likely)
- "First Responders" for identification
  - Traditional Health care providers

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Clues to a Potential Bioterrorism Attack

- Outbreak of rare or new disease
- Non-endemic distribution
- Off season occurrence
- Unusual epidemiology, clinical presentation, age distribution, antimicrobial resistance
- Genetically identical pathogens in geographically different areas

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category A - Potential Agents of Bioterrorism

Highest priority agents that pose a threat to national security because they -

- Can be easily disseminated or transmitted person to person
- Cause high mortality
- Can cause public panic and social disruption
- Require special action for Public Health preparedness

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category A - Potential Agents of Bioterrorism

Agent	Disease
Bacillus anthracis	Anthrax
Clostridium botulinum	Botulism
Fransciella tulareusis	Tularemia
Yersinia pestis	Plague
Variola major	Small pox
Vector borne viruses	Viral hemorrhagic fever

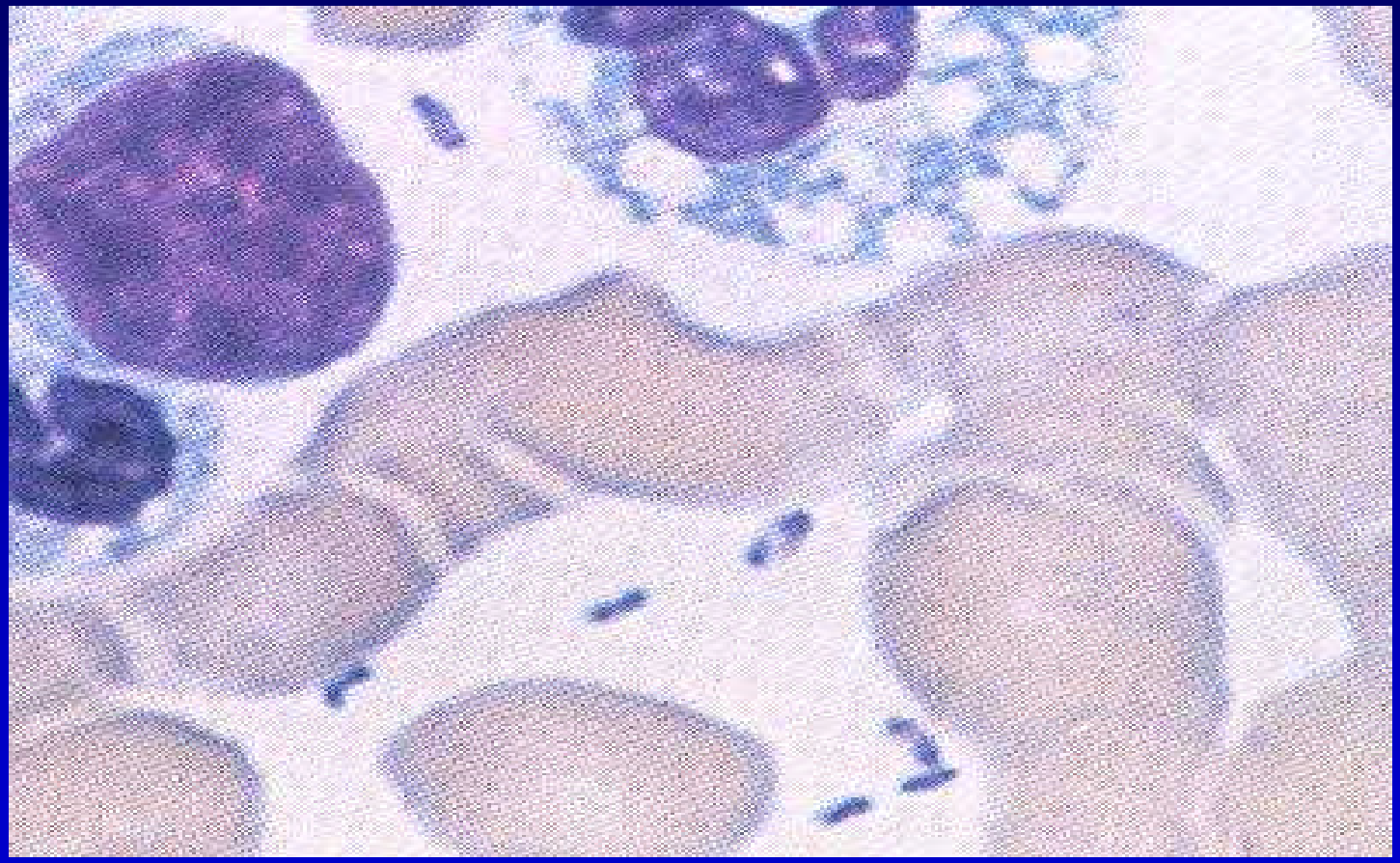
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*

Microbiology

- Family enterobacteriaceae and genus Yersinia
- Grows on blood agar and MacConkey agar
- Gram negative bipolar staining coccobacilli - non motile, non sporulating

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM



OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*

Microbiology

- Non-lactose fermenting
- Microaerophilic, indole, oxidase and urease negative

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*

Epidemiology

- Maintained in nature as a zoonotic infection in rodent hosts and fleas
- Epidemic bubonic plague described in biblical and medieval times
- Killed one fourth of Europe's population in the middle ages

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*

Epidemiology

- Most recent pandemic at the turn of 20th century originated in China
- Large outbreaks of pneumonic plague in Manchuria and India - 1910 - 1911 and 1920 - 1921
- Infected fleas released by Japan in Chinese cities - 1930's and 1940's
- Investigated as a biological weapon by Japan during WW II
- Studied by the US in the 1950's
- Other countries suspected of weaponizing plague

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*

Transmission

- Contact (bite) with fleas
- Skin to regional lymph nodes
- Bacteremia, septicemia and endotoxemia
- Shock, DIC and coma
- Respiratory droplets from animals
- Respiratory droplets from infected humans

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*

Clinical Presentations

- Classical Bubonic plague - 84%* (14%)**
- Primary septicemic plague - 13%* (22%)**
- Primary Pneumonic plague - 2%* (57%)**

*US cases 1947 - 1996

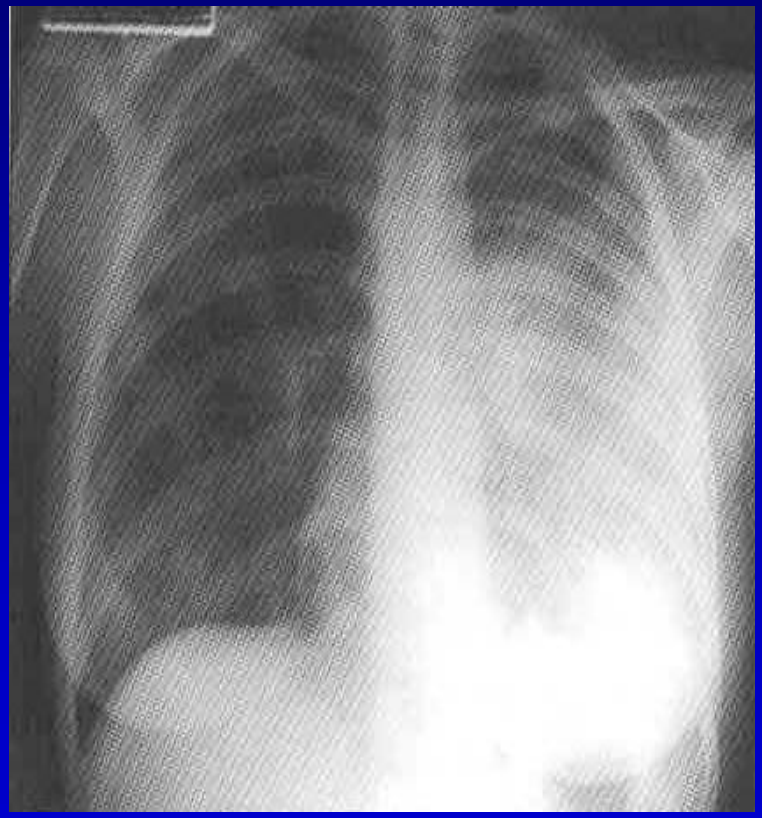
** Mortality rate

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*



OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*

Clinical Presentations

- Secondary septicemic plague
- Secondary pneumonic plague

  12% of US cases over last 50 years
- Plague meningitis
- Plague pharyngitis

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*

Natural Disease Versus Bioterrorism

- Primary pneumonic plague most likely*
- Exposure to symptoms 1 - 6 (2 - 4) days
- Fever, cough, dyspnea
- Bloody, watery or purulent sputum*
- Prominent GI symptoms**

*Hemoptysis strongly suggests plague versus anthrax

**2 recent cases contracted from cats

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*

Laboratory Diagnosis - Level A to Level B or C Lab

- Smear* and culture

  Blood, respiratory secretions, CSF

- Acute and convalescent serology - EIA, PHA, PHIA - detect antibody to F1 antigen
- Rapid Diagnostic Tests - Antigen, IGM EIA, Immunostaining, PCR

*DFA, if available, Gram, Wright, Giemsa or Wayson

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*

Antimicrobial Therapy

- Streptomycin or Gentamicin
- Tetracycline or Doxycycline
- Fluoroquinolones - In vitro and animal studies
- Chloramphenicol - Meningitis
- TMP/SMX - Sulfonamides only

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*

Antimicrobial Resistance

- Rifampin, Aztreonam, Ceftazidime, Cefotetan and Cefazolin
- Rare natural resistance to tetracyclines
- Quinolone resistance
- Multidrug resistance - Plasmid mediated
- Multidrug resistance - Engineered??

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*

Post Exposure Chemoprophylaxis

- Contact with a patient at less than 2 meters
- Prophylaxis for 7 days
- Doxycycline - First choice
- Tetracycline, sulfonamides, chloramphenicol
- Fluoroquinolones - studies in mice

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*

Vaccination

- Killed whole cell vaccine

  US 1946 - 1998

- Fusion Protein vaccine (F1-V antigen)

  USAMRIID - Mice to primates

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*

Infection Control Procedures

- Standard precautions for bubonic plague
- Strict isolation with droplet precautions for pneumonic plague - 48 hours of antibiotics/culture negative
- Surgical masks, gown, gloves, eye protection - HEPAF masks and negative pressure room - for aerosol generating procedures
- Dead bodies - routine strict precautions
- No need for environmental decontamination
- Rodent control measures, flea insecticides and flea barriers

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Potential Agents of Bioterrorism

Second highest priority agents because they

- Are moderately easy to disseminate
- Cause moderate morbidity and low mortality
- Require specific enhancement of CDC's diagnostic capacity and enhanced disease surveillance

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Bacterial Agents of Bioterrorism

Agent	Disease
Coxiella burnetti	Q Fever
Brucella species	Brucellosis
Burkholderia mallei	Glanders
Burkholderia pseudomallei	Melioidosis
Rickettsia prowazekii	Typhus Fever
Chlamydia psittaci	Psittacosis

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Q Fever - *Coxieilla burnetti*

Microbiology/Epidemiology

- Rickettsial organism - World wide zoonosis
- Cattle, sheep and goats - most common reservoirs
- Dogs, cats and birds
- No disease in infected animals
- Large number of organisms in body fluids
- Especially large number in placenta

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Q Fever - *Coxieilla burnetti*

Transmission

- Resistant to heat and desiccation
- Highly infectious by aerosol - single organism
- Human infection - Inhalation
- Raw milk or fresh goat cheese

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Q Fever - *Coxieilla burnetti*

Clinical Features

- Incubation period 2 - 14 days
- Febrile illness
- Differential diagnosis - Atypical pneumonia, HPS, Tularemia, plague
- Culture negative endocarditis, chronic hepatitis, aseptic meningitis, encephalitis, osteomyelitis

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Q Fever - *Coxieilla burnetti*

Natural Disease versus Bioterrorism

- Similar clinical presentation
- Incapacitating biowarfare agent

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Q Fever - *Coxieilla burnetti*

Laboratory Diagnosis

- IgM antibodies by ELISA - Diagnostic
- May detect by second week of illness
- IFA, ELISA and CFT - Reference laboratories
- Difficult to isolate

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Q Fever - *Coxieilla burnetti*

Antimicrobial Therapy

- All cases treated to prevent complications
- Tetracycline or doxycycline for 5 - 7 days
- Erythromycin, Azithromycin and Clarithromycin?
- Tetracycline or Doxycycline
  +
  TMP/SMX or Rifampin

  } ≥ 12 months for endocarditis
- Valve replacement

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Q Fever - *Coxieilla burnetti*

Post Exposure Chemoprophylaxis

- Immediate (1 - 7 days) - Not effective

  May prolong the onset of disease
- Tetracycline or Doxycycline (8 - 12 days) post exposure for 5 - 7 days

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Q Fever - *Coxieilla burnetti*

Vaccination

- Formalin inactivated whole cell vaccine
  - Licensed in Australia
  - Investigational in US - for at risk personnel
- Skin test required prior to vaccination
- Single dose - complete protection against natural disease
  - 95% protection against aerosol exposure within 3 weeks
- Protection for 5 years
- Live attenuated vaccine (Strain M44) - former USSR

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Q Fever - *Coxieilla burnetti*

Infection Control Procedures

- Standard precautions for health care worker
- No person-to-person transmission
- Decontamination – Soap and water or 0.5 hypochlorite

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Brucellosis - Brucella species

AKA - Undulant Fever, Mediterranean Fever, Malta Fever

Microbiology/Epidemiology

- Brucella species - 6

Human pathogens - *B melitensis* (goat)
B. abortus (cattle)
B. suis (pig)
B canis (dog)

- Facultative intracellular gram negative coccobacilli
- Natural reservoirs - Herbivores
- Septic abortion and orchitis in animals

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Brucellosis - Brucella species

Microbiology/Epidemiology

- Uncommon in the US - 0.5 cases per 100,000 population
  - Abbattier and veterinary workers
  - Unpasteurized dairy products
- Highly endemic - Southwest Asia (128 per 100,000)
  - Hazard to military personnel

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Brucellosis - Brucella species

Transmission

- Stable to environmental conditions
- Long persistence in wet ground and food
- Ingestion - Infected raw milk or meat
- Inhalation - Contaminated aerosol

  Highly infectious

  10 - 100 bacteria
- Contact - Skin

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Brucellosis - Brucella species

Clinical Features

- Incubation period 8 - 14 days (5 - 60 days)
- Nonspecific febrile illness
- Lumbar pain and tenderness - 60%

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Brucellosis - Brucella species

Clinical Features

- GI symptoms - 7%
- Hepatosplenomegaly - 45 - 63%
- Sequale- Osteoarticular infections, Hepatitis, meningitis, encephalitis, endocarditis, pancytopenia

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Brucellosis - Brucella species

Natural Disease versus Bioterrorism

- Natural disease prolonged, incapacitation and disabling
- Mortality rate 5% - Untreated
  - Endocarditis or meningitis
- Intentional large aerosol
  - Shorter incubation
  - Higher clinical attack rate
- Weaponized by the US in 1954

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Brucellosis - Brucella species

Laboratory Diagnosis

- Blood cultures - 15 - 70%
- Bone marrow culture - 92%
- Longer incubation
- Slow growing oxidase positive colonies — Level A
- Small faintly staining GNB — Level B or C

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Brucellosis - Brucella species

Laboratory Diagnosis

- Acute and convalescent serology
- SAT - IGM and IGG

  Single titer ≥ 1:160 active disease
- ELISA and PCR becoming available

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Brucellosis - Brucella species

Antimicrobial Therapy

- Doxycycline + Rifampin - 6 weeks
- Doxycycline 6 weeks + Streptomycin 2 - 3 weeks
- TMP/SMX - Less effective
- Tetracycline + Rifampin + Streptomycin for long term therapy - Endocarditis or meningoencephalitis

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Brucellosis - Brucella species

Post-Exposure Chemoprophylaxis

- Not generally recommended
- High risk exposures*

3 - 6 weeks of one of treatment regimens

*Vaccine - Needlestick
*Laboratory exposure
*Bioterrorism

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Brucellosis - Brucella species

Vaccination

- Live vaccine for animals
  - Widely used
  - Eliminated from domestic herds in the US
- No licensed human vaccine in the US
- *B. abortus* (S19-BA) - USSR and China
  - Limited efficacy and annual revaccination

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Brucellosis - Brucella species

Infection Control Procedures

- Standard precautions for health care workers
- Rare person-to-person transmission - Tissue transplantation and sexual contact
- BSL - 3 Laboratory practices
- Environmental decontamination - 0.5% hypochlorite

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Melioidosis - *Burkholderia pseudomallei*

Microbiology/Epidemiology

- Gram negative bacilli “safety pin” appearance
- Widely distributed in the soil and water in tropics
- Endemic in Southeast Asia and Northern Australia

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Melioidosis - *Burkholderia pseudomallei*

Transmission

- Widely distributed
- Common cause of community-acquired septicemia in northeastern Thailand
- Inhalation
- Contaminated injuries
- Long incubation period - Imported

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Glanders - *Burkholderia mallei*

Microbiology/Epidemiology

- Gram negative bacilli - “Safety pin” appearance
- Occurs primarily in horses, mules and donkeys
- Acute form - Mules and donkeys
- Chronic form or Farcy - Horses
- Human disease uncommon
- Not found in water, soil or plants

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Glanders - *Burkholderia mallei*

Transmission

- Veterinarians and animal handlers
- Low transmission rate - low concentration, less virulence
- Inhalation
- Contaminated injuries

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Glanders - Melioidosis

Clinical Features

- Incubation period - 10 - 14 days
- Acute pneumonic illness*
- Acute fulminant septicemic illness*
- Acute oral, nasal, conjunctional infections
- Chronic - Skin and muscle abscesses, osteomyelitis, meningitis and brain abscess
- Reactivation disease

*Expected in case of bioterrorism

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Glanders - Melioidosis

Natural Disease versus Bioterrorism

- WW I - Glanders spread by central powers - Russian horses and mules
- Human cases in Russia increased during and after WW I
- WW II - Japanese infected horses, civilians and POWs in China
- US studied B.mallei and B. pseudomallei as BW agents - 1943 - 1944 - Not weaponized

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Glanders - Melioidosis

Natural Disease versus Bioterrorism

- USSR believed to be interested/experiments
- Aerosols (cultures) - highly infectious to laboratory workers*
- Shorter incubation period
- Acute pneumonic or septicemic illness

*Recent case - Military Research Microbiologist

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Glanders - Melioidosis

Laboratory Diagnosis

- Gram stain
- Irregular staining - methylene blue or Wright's stain
- Culture - Standard methods
- Serology - Agglutination
  Complement Fixation
  More specific ≥ 1:20
  Single titers > 1:160 active infection

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Glanders - Melioidosis

Antimicrobial Therapy

- Oral tetracycline, amoxacillin/clavulante or TMP/SMX for localized disease for 60 - 150 days
- I/V ceftazidime + TMP/SMX for 2 weeks - PO TMP/SMX for 6 months

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Glanders - Melioidosis

Post Exposure Chemoprophylaxis

- TMP/SMX Trial

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Glanders - Melioidosis

Vaccination

No vaccine for human use

No vaccine for animal use

Candidate vaccines

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Glanders - Melioidosis

Infection Control Procedures

- Standard precaution for health care workers
- BSL 3 practices in the laboratory

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Viral Agents of Bioterrorism

Agent	Disease
Venezuelan Encephalitis virus	Febrile illness - Encephalitis
Eastern Equine Encephalitis virus	Encephalitis
Western Equine Encephalitis virus	Encephalitis

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Viral Agents

- Mosquito-borne Alpha viruses
- VEE, WEE, EEE
- Difficult to distinguish clinically
- Encephalitis in horses, mules and donkeys precedes human cases
- VEE acute febrile illness - Encephalitis less common

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Viral Agents

- EEE and WEE - Encephalitis predominantly
- No evidence for horse-to-human or human-to-human transmission
- Diagnosis - Virus isolation, serology, PCR
- No natural aerosol transmission
- Infective dose of VEE is 10 - 100 organisms
- Viruses killed by heat and standard disinfectants

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Viral Agents

- Stable during storage and manipulation
- VEE tested as a BW agent by the US in 1950's and 1960's
- In a bioterrorism event - Human cases precede or concurrent with animals
- No specific therapy

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Viral Agents

- Alpha interferon and poly ICLC - Effective post exposure prophylaxis in experimental animals
- Live attenuated vaccine - IND
- Formalin-inactivated vaccine – IND*
- Standard precautions and vector control

*Booster immungen

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B – ToxinAgents of Bioterrorism

Agent	Disease
Ricin	Necrosis - ARDS
Epsilon Toxin	Cytotoxic - ARDS
Staphylococcal Enterotoxin B	Cytokines - ARDS
T2 - Mycotoxins	Dermal, Ocular, Respiratory and GI

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Biological Toxins

Ricin Toxin

- Beans of castor plant (*Ricinus cummunis*)
- Ubiquitous plant
- Toxin highly stable and easy to extract
- Protein cytotoxin
- Toxic by multiple routes
- Inhalation - ARDS (1 -3 days) - Death

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Biological Toxins

Ricin Toxin

- Ingestion - GI, hepatic, splenic and renal necrosis
- IM injection - Necrosis of muscle and regional lymph nodes

  Moderate visceral involvement
- Antigen detection by ELISA - serum and respiratory secretions
- Paired serology

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Biological Toxins

Ricin Toxin

- PCR - Castor bean DNA
- No specific therapy
- Gastric lavage and cathartics
- Charcoal - Not useful
- Protective mask for inhalation

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Biological Toxins

Ricin Toxin

- Standard precautions for health care workers
- Hypochlorite (0.1% sodium hypochlorite) solution inactivates ricin
- Immunization - Promising in animal models

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Biological Toxins

Epsilon (Alpha) Toxin

- *C. perfringens* - 12 toxins
- One or more can be weaponized
- Alpha toxin - highly toxic phospholipase
- Inhalation - ARDS
- Thrombocytopenia and hepatic damage
- Immunoassay for toxin

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Biological Toxins

Epsilon (Alpha) Toxin

- Bacteria cultured easily
- Penicillin the antibiotic of choice
- Clindamycin or rifampin - Reduce toxin
- Veterinary toxoids widely used
- Toxoids for enteritis necroticans - humans

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Biological Toxins

Staphylococcal Enterotoxin B

- SEB - one of the exotoxins produced by S. aureus
- Protein (23-29 kd)
- Pyrogenic and GI toxicity
- Food poisoning - Improperly handled or refrigerated food
- Inhaled SEB - Lower dose (1/100th) toxic

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Biological Toxins

Staphylococcal Enterotoxin B

- ARDS - Within 12 hours
- Concomitant GI symptoms
- Contamination of food or small volume water supplies
- One of 7 agents in the US BW program prior to 1969

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Biological Toxins

Staphylococcal Enterotoxin B

- No specific therapy
- Experimental immunization reported
- A candidate human vaccine - advanced development
- Standard precautions for health care workers
- Decontamination - Soap and water
- Destroy contaminated food

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Biological Toxins

T-2 Mycotoxins

- Trichothecene mycotoxins - Over 40
- Fusarium, Myrotecium, Trichoderma, Stachybotrys and others
- “Yellow Rain” - pigmented oily fluids
- Extremely stable in the environment
- Resist hypochlorite and autoclaving

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Biological Toxins

T-2 Mycotoxins

- Dermal, ocular, respiratory and GI exposures
- Rapid and severe symptoms
- No specific therapy – Superactivated charcoal if swallowed
- Decontamination - soap and water

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Biological Toxins

T-2 Mycotoxins

- Contact precautions - Standard precautions for health care workers
- Environmental decontamination

  1% sodium hypochloride and 0.1 NAOH with 1 hour contact time

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Biological Toxins

Other Toxins - Potential for Bioterrorism

- Tetanus toxin - *C. tetani* - Tetanus
- Saxitoxin - paralytic shellfish poisoning
- Tetrodotoxin - fish, frogs, etc.
- Toxins - Blue green algae
  - Anatoxin – A (s)
  - Microcystin

AGENTS OF BIOTERRORISM OVERVIEW OF POTENTIAL

Category B - Food and Waterborne Agents

Agents	Disease
Salmonella species	Enteritis
	Typhoid Fever
Shigella dysenteriae	Dysentery
E. coli 157:H7	Bloody Diarrhea
Vibrio cholerae	Cholera
Cryptosporidium parvum	Diarrhea

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category C - Potential Agents of Bioterrorism

Third highest priority agents include emerging pathogens that could be engineered for mass dissemination

- Availability
- Ease of production and dissemination
- Potential for high morbidity and mortality
- Major health impact

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category C - Potential Agents of Bioterrorism

Nipah virus

Hantavirus

Tickborne Hemorrhagic Fever viruses

Tickborne encephalitis viruses

Yellow Fever

Multidrug resistant Tuberculosis

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category C - Potential Agents of Bioterrorism

Nipah Virus

- Outbreak in Malaysia - 1998 - 1999
- 1 Million deaths in swine
- Encephalitis in 265 humans
- Direct contact with swine
- Mortality rate - 40%
- Eradicated from swine

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category C - Potential Agents of Bioterrorism

Nipah Virus

- Likely to be present in fruit bats
- Human to human transmission not documented
- No cases documented in the US

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category C - Potential Agents of Bioterrorism

Tickborne Encephalitis Viruses

Far Eastern, Central European,

Kyasanur Forest, Louping ill, Powassan and Negishi

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category C - Potential Agents of Bioterrorism

Tickborne Hemorrhagic Fever Viruses

Crimean-Congo Hemorraghic Fever

Omsk Hemorrahgic Fever

Kyasanur Forest Disease

AGENTS OF BIOTERRORISM OVERVIEW OF POTENTIAL

Detection

Biological Integrated Detection System (BIDS)

Long Range Biological Stand Off Detection System - (LRBSDS)

Short Range Biological Stand Off Detection System - (SRBSDS)

AGENTS OF BIOTERRORISM OVERVIEW OF POTENTIAL

Personal Protection

Protective Mask - M40*

Battle Dress Overgarment (BDO)

Protective Gloves

Overboots

*HEPA-filter masks or surgical mask protection against BWs but not CWs

AGENTS OF BIOTERRORISM OVERVIEW OF POTENTIAL

Decontamination

- Mechanical Decontamination
  - Water filtration
  - Air filtration

AGENTS OF BIOTERRORISM OVERVIEW OF POTENTIAL

Decontamination

- Chemical Decontamination
  - M291 Skin Decontamination Kit
  - Soap and water
  - Hypochlorite solution
    - 0.5% for 10 - 15 minutes for gross contamination*
    - 5% for clothing or equipment

*Except open body cavity wound, brain and spinal cord injuries

AGENTS OF BIOTERRORISM OVERVIEW OF POTENTIAL

Decontamination

Physical Decontamination

- Dry Heat (160^0C) for 2 hours
- Autoclaving (121^0C) for 20 minutes
- Solar Ultraviolet radiation

AGENTS OF BIOTERRORISM OVERVIEW OF POTENTIAL

Patient Isolation Precautions

Standard Precautions - All patients

- Handwashing
- Gloves*
- Mask*, eye protection*, face shield*
- Patient care equipment and linen

*As needed

AGENTS OF BIOTERRORISM OVERVIEW OF POTENTIAL

Patient Isolation Precautions

Contact Precautions - Standard Precautions Plus

- Private room - Cohort same infection
- Gloves when entering
- Gown when entering
- Limit movement or transport of the patient
- Patient care items - Surfaces - Daily cleaning
- Dedicate noncritical patient care equipment or disinfect between patients

AGENTS OF BIOTERRORISM OVERVIEW OF POTENTIAL

Patient Isolation Precautions

Contact Precautions

Conventional Diseases

MRSA, VRE, *C. difficile*

RSV, Parainfluenza, Enteroviruses

Enteric Infections – Incontinence

SSSS, HSV, Impetigo, Lice, Scabies

Hemorrhagic conjunctivitis

Biothreat Diseases

Viral Hemorrhagic Fevers

Draining anthrax lesions

AGENTS OF BIOTERRORISM OVERVIEW OF POTENTIAL

Patient Isolation Precautions

Droplet Precautions - Standard Precautions Plus

- Private room - Cohort with same infection or maintain 3 feet between patients
- Mask - Within 3 feet of patient
- Limit movement and transport of the patient - place mask if needed

AGENTS OF BIOTERRORISM OVERVIEW OF POTENTIAL

Patient Isolation Precautions

Droplet Precautions

Conventional Diseases	Biothreat Diseases
Invasive *H. influenzae* disease	
Invasive Meningococcal disease	Pneumonic plague
Drug resistant pneumococcal disease	
Diphtheria – Pertussis - Mycoplasma	
Group A streptococcus	
Influenza - Rubella - Mumps -	Parvovirus

AGENTS OF BIOTERRORISM OVERVIEW OF POTENTIAL

Patient Isolation Precautions

Airborne Precautions - Standard Precautions Plus

- Monitored negative air pressure room
- Respiratory protection on entry
- Limit movement and transport of the patient - place mask if needed

AGENTS OF BIOTERRORISM OVERVIEW OF POTENTIAL

Patient Isolation Precautions

Airborne Precautions

Conventional Diseases	Biothreat Diseases
Measles	
Varicella	Small Pox
Pulmonary TB	

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Preparedness for Public Health and Medical Communities

- CDC * - Designated by DHHS
- Cooperative agreements with states and large cities
- Five areas emphasized (1999 - 2001)
    - i) Preparedness, planning and readiness assessment
    - ii) Surveillance and epidemiology capacity
    - iii) Biological laboratory capacity
    - iv) Chemical laboratory capacity
    - v) Health alert network and training

*Disease reporting - a tool for preparedness

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Preparedness for Public Health and Medical Communities

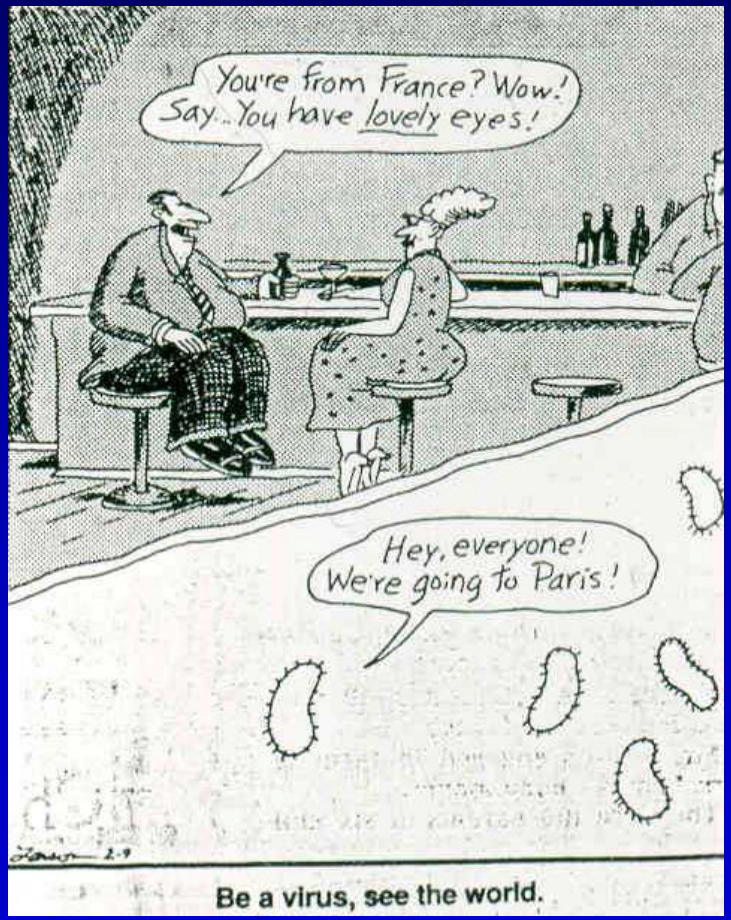
- Dept of Defense – Federal Effort
- Trained first responders in 120 cities
- Handed over to Dept of Justice – 2000

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Preparedness for Public Health and Medical Communities

- FDA - Interagency group
- USAMRIID - Aeromedical isolation team
- ACP/ASIM - Pocket guide
- APIC - CDC - Bioterrorism Readiness plan
- County and City level preparedness
- Small town level preparedness
- Detection of clusters - AACERDAIC
- Immediate Immunity - Passive Antibody Administration
- Executive order – 13139 – September, 1999

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM



OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Global Alert and Response

WHO

- Privileged Access
- Geographic Resources
  - Headquarters Geneva
    - Regional Offices - 6
    - Country Offices - 141

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Global Alert and Response

WHO

Collaborating Centers

Laboratories and Institutions - 250

- CDC
- USAID
- Do D-GEIS*
- Counterparts in other countries

*US Dept of Defense Global Emerging Infections Surveillance and Response System

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Global Alert and Response

WHO

- Surveillance Networks
  - Electronic “detective” system* and databases
  - International health regulations

*FluNet (> 50 yrs) 110 labs in 84 countries

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Global Alert and Response

WHO

- Welcome Assistance

- "Deep" Experience

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Global Alert and Response

WHO - Surveillance and Response

- Containing Known Risks
- Responding to the Unexpected

Semiautomatic electronic system

Health Canada

US based Pro-MED

Local online newspapers

Scan the world-outbreak verification

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Global Alert and Response

WHO - Surveillance and Response

- Global outbreak alert and Response Network
  April 2000
- Standardized procedures
- Communication
- Guidelines for foreign nationals

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Global Alert and Response

WHO - Surveillance and Response

Improving Preparedness

HealthMap

NASA and Other Satellites

TEPHINET - CDC Training Program*

Lyon, France - 2001 - Specialized training program

*Training program in Epidemiology and Public Health Interventions Network

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Global Alert and Response

WHO - Surveillance and Response

- Improving Preparedness
  - Long term preparedness working group
  - Early Warning and Response Network (EWARN)
  - Capacity building - National epidemic detection
  - Births and Deaths Registry

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Global Alert and Response

WHO - Preparedness for Bioterrorism

- Updated Standard Guide
- Epidemiological techniques for natural outbreak
- Exchange between Public health and Veterinary Sectors
- Overseeing remaining stocks of small pox virus

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Global Alert and Response

WHO - Proactive Role

- Consensus resolution - World Health Assembly
- Investigate and verify outbreaks prior to official notification
- Global solutions for Global causes and consequences

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Global Alert and Response

WHO - US Support

- CDC*
- USAID - First Global Strategy for Containment of Antimicrobial Resistance
- NIH* - Fogarty International Center
- Bureau of PRM - Malaria control

*Grants to Global Outbreak Alert and Response Network and WHO collaborating Centers

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Economic Impact

- Brucellosis scenario - 477.7 million/100,000 exposed
- Anthrax scenario - 26.2 billion/100,000 exposed
- Post attack prophylaxis program
- Rapid implementation
- Single most important means - reducing losses
- Economic justification*

*Kaufman et al, EID, April - June 1997

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Preparedness for Public Health and Medical Communities

Balance

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Preparedness for Public Health and Medical Communities

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Nature's Biowarfare

"Modern adventurers like to up the ante, but even the most extreme sports wouldn't produce the adrenaline of a race against pandemic influenza or a cloud of anthrax at the Super Bowl. In the field of Infectious Diseases, reality is stranger than anything a writer could dream up. The most menacing bioterroist is Mother Nature herself."

Secret Agents: The Menace of Emerging Infections, by Madeline Drexler, John Henry Press, 2002

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

THE NEXT PRESENTATION

Laboratory Diagnosis of Biological Weapons: Conventional and New Methods

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