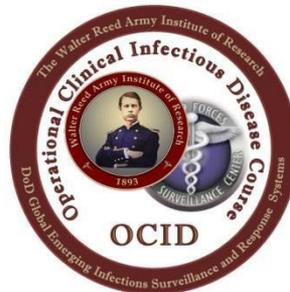


Biothreats in the Tropics

WRAIR- GEIS 'Operational Clinical Infectious Disease' Course



UNCLASSIFIED

Acknowledgments

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Disclaimer

The views expressed in this presentation are those of the speaker and authors, and do not reflect the official policy of the Department of Army, Department of Defense, or U.S. Government

Introduction

- Biothreat infections
- Types of biothreats in the tropics and travelers' concern
- BW and bioterrorism
- Brucellosis
- Plague
- Anthrax
- Melioidosis
- Tularemia
- For each: introduction, epidemiology, signs and symptoms, diagnosis and differential diagnosis, treatment, and prevention

Current Biothreat List (CDC)

Category A:

- Anthrax
- Botulinum toxin
- Plague
- Smallpox
- Tularemia
- Viral Hemorrhagic Fevers (Junin, Machupo, Lassa, Hanta, RVF, CCHF, Dengue, Ebola, Marburg)

Category C:

- Nipah & Hendra viruses
- More hantaviruses
- Tickborne HFVs (OHFV, etc.)
- Tickborne encephalitis flaviviruses
- Yellow fever
- TB, MDR TB
- Other rickettsiae
- Rabies
- Chikungunya, etc.

Category B:

- Melioidosis
- Q fever
- Brucellosis
- Glanders
- Psittacosis
- Ricin toxin
- Epsilon toxin (*Clostr. perfringens*)
- *Staphylococcus* enterotoxin B
- Typhus fever (*Rick. prowazekii*)
- Food- & waterborne pathogens (bacteria, viruses (caliciviruses, hepatitis A), *Protozoa* (*Cryptosporidium*, *Cyclospora*, etc.))
- Mosquito-borne viral encephalitides (WNV, LACV, CEV, VEE, EEE, WEE, JE, SLEV)

Can be or have been used for BW or bioterrorism

Explaining the Categories

Category A – high-priority agents, pose the highest risk to the public and national security because:

- They can be easily spread or transmitted from person to person
- Result in high death rates and have the potential for major public health impact
- Might cause public panic and social disruption
- Require special action for public health preparedness

Category B – the 2nd highest priority because:

- They are moderately easy to spread
- Result in moderate illness rates and low death rates
- Require specific enhancements of CDC's lab capacity and enhanced disease monitoring

Category C – 3rd highest priority agents, include emerging pathogens that could be engineered for mass spread in the future because:

- They are easily available
- Easily produced and spread
- Potential for high morbidity and mortality rates and major health impact

Diseases from CDC Webpage for Travelers

[African Tick-Bite Fever](#)

[African Trypanosomiasis](#)

[Avian Flu \(Bird Flu\)](#)

[Chagas Disease](#)

[Chikungunya](#)

[Dengue](#)

[Diphtheria](#)

[Ebola](#)

[Flu \(Influenza\)](#)

[HIV](#)

[Hand, Foot, and Mouth Disease](#)

[Hepatitis A](#)

[Hepatitis B](#)

[Hepatitis C](#)

[Hepatitis E](#)

[Japanese Encephalitis](#)

[Leptospirosis](#)

[Malaria](#)

[Measles](#)

[Meningococcal Disease](#)

• [Mumps](#)

• [Murray Valley Encephalitis virus](#)

• [Pertussis \(Whooping Cough\)](#)

• [Plague](#)

• [Pneumococcal Disease](#)

• [Polio](#)

• [Rabies](#)

• [Rift Valley Fever](#)

• [Ross River virus disease](#)

• [Routine Vaccines](#)

• [Rubella](#)

• [Scabies](#)

• [Schistosomiasis](#)

• [Tetanus](#)

• [Tick-borne Encephalitis](#)

• [Tuberculosis \(TB\)](#)

• [Typhoid Fever](#)

• [West Nile virus](#)

• [Yellow Fever](#)

• [Zika](#)

**Biothreat infections
For February, 2016:
18/39 (46%)**

Fever in returned travelers presenting in the United Kingdom: Recommendations for investigation and initial management.

Table 2 Common or important causes of fever associated with geographical areas and specific risk factors.

Risk factor	Common	Occasional	Rare but important
<i>Geographical area</i>			
Sub-Saharan Africa	HIV-associated infections (inc seroconversion) Malaria Rickettsiae	Acute schistosomiasis (Katayama) Amoebic liver abscess Brucellosis Dengue Enteric fever Meningococcus	Histoplasmosis Other arbovirus, e.g. Rift Valley, West Nile fever, Yellow fever Trypanosomiasis Viral haemorrhagic fever (Lassa, Ebola, Marburg, CCHF) Visceral leishmaniasis
North Africa, Middle East and Mediterranean		Brucellosis Q fever Toscana (sandfly fever)	Visceral leishmaniasis
Eastern Europe and Scandinavia		Lyme Disease	Hantavirus Tick-borne encephalitis Tularaemia
South and Central Asia	Dengue Enteric fever Malaria	Chikungunya Visceral leishmaniasis	CCHF Japanese encephalitis Other arbovirus (Nipah virus) Rickettsiae
South East Asia	Chikungunya Dengue Enteric fever Malaria	Leptospirosis Meliodosis	Hantavirus Japanese encephalitis Other arbovirus (Nipah virus) Paragonomiasis Penicilliosis Scrub typhus
North Australia		Dengue Murray Valley Q fever Rickettsiae Ross River fever	Barmah Forest Meliodosis
Latin America and Caribbean	Dengue Enteric fever Malaria	Brucellosis Coccidioidomycosis Histoplasmosis Leptospirosis	Acute trypanosomiasis (Chagas') Hanta virus Yellow fever
North America		Coccidioidomycosis Histoplasmosis Lyme disease Rocky Mounted Spotted fever	Babesiosis Ehrlichiosis West Nile fever
<i>Specific risk factors</i>			
Game parks	Tick typhus		Anthrax Trypanosomiasis
Fresh-water exposure		Acute schistosomiasis (Katayama) Leptospirosis	
Caves		Histoplasmosis	Rabies Ebola
HIV	Amoebiasis Non-typhoid salmonella Tuberculosis	STI, e.g. syphilis Visceral leishmaniasis	Blastomycosis dermatitidis Coccidioidomycosis Histoplasmosis Penicilliosis

Abbreviations: CCHF, Congo Crimean haemorrhagic fever; STI, sexually transmitted infections.

Causes of fever by geography, specific risks

Areal/Risk	Common	Occasional	Rare but important
Sub-Saharan Africa	HIV-associated infections (inc. seroconversion) Malaria, Rickettsiae	Acute schistosomiasis Amebic liver abscess Brucellosis Dengue Enteric fever Meningococcus	Histoplasmosis Arbovirus (RVF, WNF, YF) Trypanosomiasis VHFs (Lassa, Ebola, Marburg, CCHF) Visceral leishmaniasis
North Africa, Middle East, Mediterranean		Brucellosis Q fever Toscana (sandfly fever)	Visceral leishmaniasis
Eastern Europe, Scandinavia		Lyme Disease	Hantavirus Tick-borne encephalitis Tularemia
South and Central Asia	Dengue Enteric fever Malaria	Chikungunya Visceral leishmaniasis	CCHF JE Other arbovirus (Nipah) Rickettsiae
South East Asia	Chikungunya Dengue Enteric fever Malaria	Leptospirosis Melioidosis	Hantavirus JE Other arbovirus (Nipah) Paragonomiasis Penicilliosis Scrub typhus

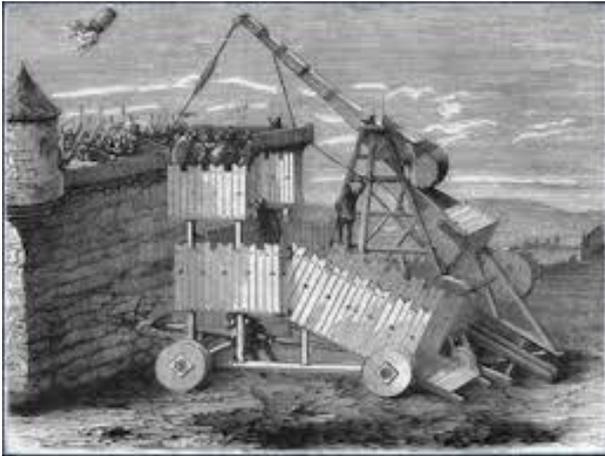
Causes of fever by geography, specific risks (cont.)

Areal/Risk	Common	Occasional	Rare but important
North Australia		Dengue Murray Valley Q fever Rickettsiae Ross River Fever	Barmah Forest Meliodosis
Latin America, Carribean	Dengue Enteric fever Malaria	Brucellosis Coccidioidomycosis Histoplasmosis Leptospirosis	Acute trypanosomiasis Hanta virus Yellow fever
North America		Coccidioidomycosis Histoplasmosis Lyme Disease RMSF	Babesiosis Ehrlichiosis WNF
Game parks	Tick typhus		Anthrax Trypanosomiasis
Fresh-water exposure		Acute schistosomiasis Leptospirosis	
Caves		Histoplasmosis	Rabies Ebola
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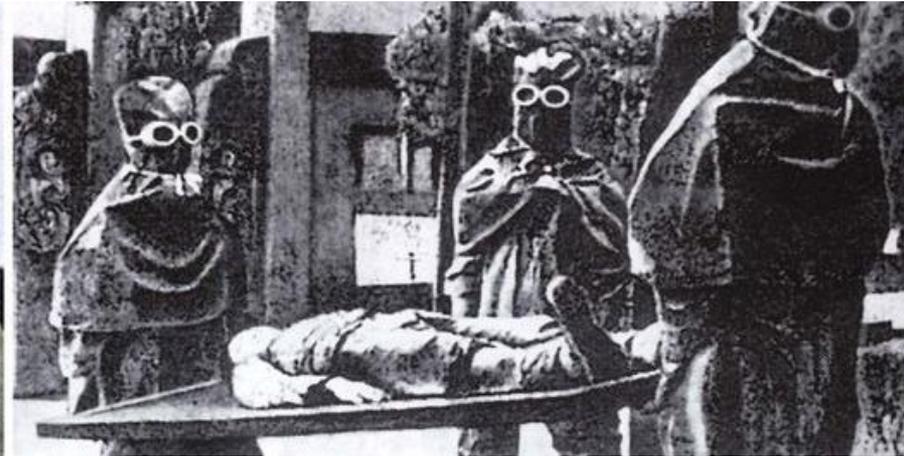
History of Weaponization

- Ca. 12th-15th centuries BC: Hittites drove infected (plague? tularemia?) animals and people to the enemy's territory trying to spread the contagion
- 1346: Tartar army in the siege of Kaffa (Feodosia) used corpses of plague victims as BW
- 1763: Jeffery Amherst ordered his troops to provide Indians loyal to the French with smallpox-laden blankets
- 1937-1945 BW program, Japan: Gen. Shiro Ishii, Unit 731 – ca. 3,000 human deaths
- 1943-1969: US R&D BW Program (agents of anthrax, tularemia, brucellosis, Q fever, VEE, botulinum toxin, SEB)
- 1920s-1992: Soviet R&D BW Program (agents of plague, anthrax, tularemia; smallpox and Marburg viruses)
- 1972: Geneva Convention but: “yellow rain”, Georgi Markov assassination, after-9/11 attacks, etc.

History of Weaponization (cont.)



Siege of Kaffa



Shiro Ishii and Unit 731



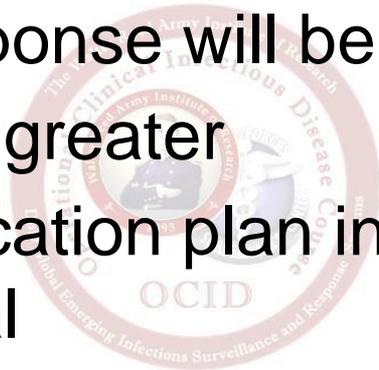
Soviet bioweapon program

After-9/11 bioterrorist attack in the US

Sources: <http://firsttoknow.com>, <http://sometimes-interesting.com>, <http://cns.miis.edu>, <http://www.nydailynews.com>

Recognition of and Preparation for Biological Attack

- Similar to that of any infectious disease outbreak **but:**
- Surveillance and response will be much more intensive
- Public anxiety will be greater
- Sound risk-communication plan involving public health authorities will be vital
- Strong public-health infrastructure with an effective epidemiologic investigative capability, practical training programs and preparedness plans will be essential

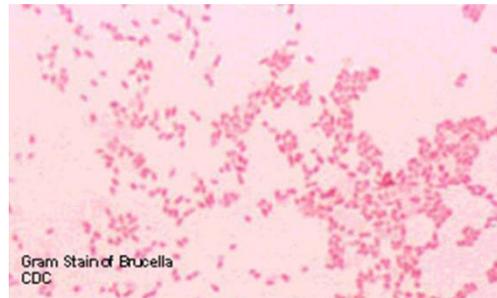


Epidemiologic Clues of a BW or Terrorist Attack:

- Large epidemic, similar disease, esp. in discrete population
- Many cases of unexplained diseases or deaths
- More severe cases, failure to respond to standard therapy
- Unusual routes of exposure, e.g. inhalational for diseases that normally occur through other exposures
- Disease unusual for given geographic area
- Serial epidemics of different diseases
- Unusual strains, genotypes or antimicrobial patterns
- Claims by terrorist groups, discovery of special munitions

Brucellosis: Introduction

- Zoonotic infection with worldwide distribution, often acquired via consumption of dairy products from infected animals
- Economically important disease of domesticated animals
 - Infectious abortion in ruminant livestock, sterility in swine and dogs
 - Infects wild animals as well; forms a reservoir
- Protean manifestations and chronic infection in humans
- Bacteriology:
 - Small, aerobic, nonmotile, nonsporulating, Gram-negative coccobacilli
 - Slow-growing in culture
 - Intracellular pathogen



Brucella species

Species

B. melitensis

B. suis

B. abortus

B. canis

B. ovis

B. neotomae

B. maris

(4 more, in all 11)

Usual Host

sheep, goats

swine

cattle

dogs

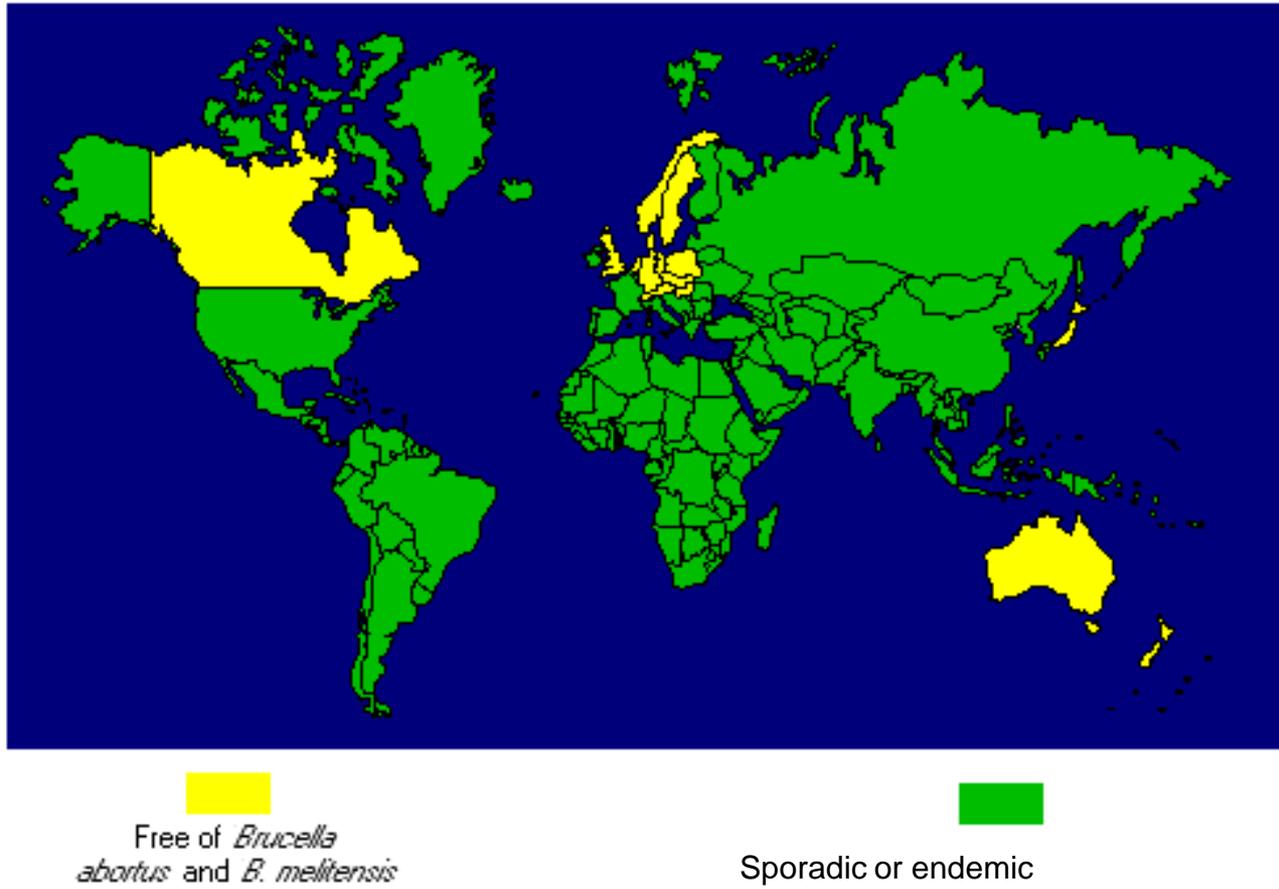
sheep

rodents

marine mammals



Brucellosis: Epidemiology



Highest prevalence: Mediterranean basin, Arabian peninsula, Central and South America (also high in Central Asia). Source: www.fao.org

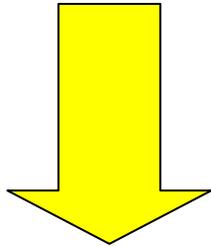
Brucellosis: Transmission

- Most humans (>500,000 cases a year) get infected from animals
 - Dairy from infected animals
 - Occupational: veterinarians, abattoir workers, ranchers
 - Recreational: hunters
 - Lab-acquired infections
 - Human-human sexual transmission extremely rare
- Modes:
 - Ingestion of raw milk, cheese, other dairy; raw meat, liver or blood
 - Contact with infected animal/secretions
 - Parturition/abortion materials highly infectious ($\leq 10^{10}$ bacteria/g); viable in placental remains ≥ 20 weeks
 - Aerosol transmission:
 - Inhalation: Infectious dose = 10 to 100 organisms
 - Inoculation of conjunctiva



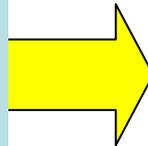
Brucellosis: Clinical Presentation

Exposure



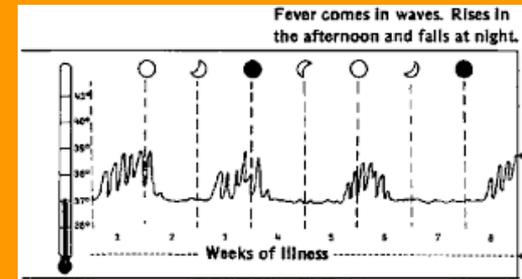
**Incubation
Period**

**2-4 Weeks
(Insidious)**



- Frequently presents as fever of unknown origin (FUO)
- Symptoms often general and Nonspecific

Non-Specific Febrile Illness

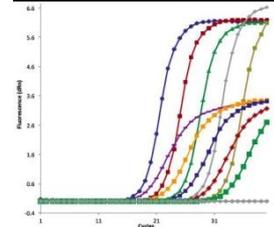
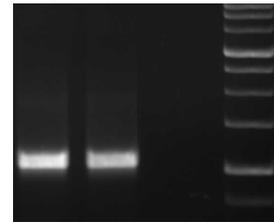
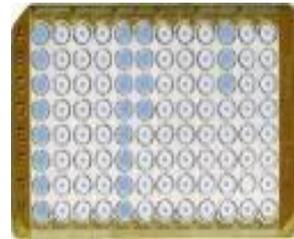


Most Common Symptoms

- Night sweats (40-90%)
- Fever (90-95%)
- Malaise/lethargy (80-85%)
- Myalgias (40-70%) – esp. of the back
- Headache, chills, anorexia
- Established infection (>2 months) often results in “undulant” fever
- Subacute and chronic: arthritis, spondylitis, osteomyelitis, hepatitis (any organ can be affected)

Brucellosis: Diagnosis

- Culture – **isolation of organism** for definitive diagnosis
 - May require prolonged incubation
 - Best yield from blood, bone marrow
 - Occasional culture from tissues, cerebrospinal fluid, joint aspirate, urine if focal infection
 - *****LABORATORY HAZARD*****
- Serology – most common method of diagnosis
 - Standard Agglutination Test – standard globally
 - **Four-fold rise** or single titer $\geq 1:160$
 - Cross-reaction to some other bacterial pathogens
 - ELISA, Coombs test and **immunofluorescence**
- PCR tests require thorough sample preparation and may be positive for months or years in a recovered person but:
- Our data – indirect phage-based *Brucella* detection



Brucellosis: Treatment

- Oral antibiotics for 4-6 weeks
 - Doxycycline (100 mg bid) + rifampin (600-900 mg/d qd)
 - Ofloxacin or cipro + rifampin or trimethoprim/sulfamethoxazole
 - TMP/SMX + rifampin
 - Doxycycline, rifampin and co-trimoxazole for neurobrucellosis
 - IM Streptomycin (1 g qd) or Gentamycin for the first 2-3 weeks
 - Combined IV and oral (IV for 1st 1-2 wk)
 - Post-exposure prophylaxis: 4-6 weeks of doxycycline + rifampin for high-risk lab or intentional aerosol release (not recommended for animal exposures)
- MDR strains!**



Brucellosis: Prevention

- Pasteurize all dairy for human consumption
- Use proper procedure and PPE in clinical laboratories in endemic areas: BSCs, respirators
- Use fastidious hygiene in milk production
- Use proper PPE when handling livestock abortion products, treating sick animals
- Vaccine: Human vaccine is not available - even in IND
- Veterinary vaccination combined with test and slaughter for control

Plague: Introduction

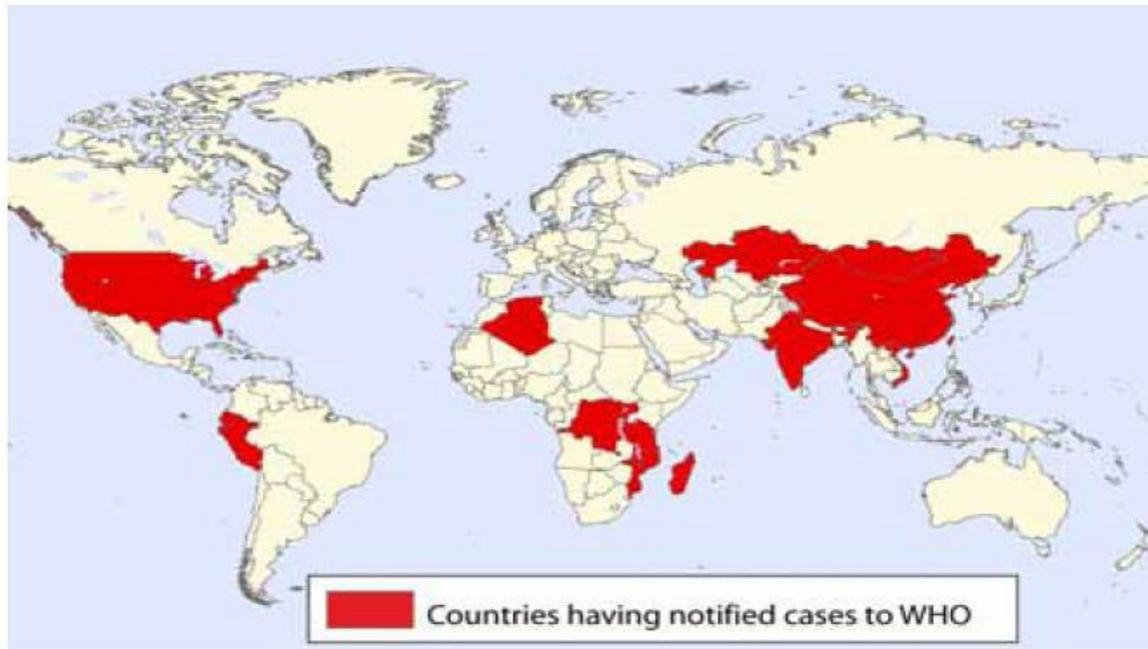
- Historically ~200 million deaths
- Biblical (I Samuel, 5:9): “Rats appeared in the land, and death and destruction were throughout the city...young and old, with an outbreak of tumors in the groin.”
- Major Pandemics:
 - 541 AD - Plague of Justinian
 - 1346 AD - ‘Black Death’ (**proven by paleogenomics**)
 - 1894 AD - Modern Pandemic
- *Yersinia pestis*
 - Family Enterobacteraceae
 - Gram-negative, non-motile bacillus
 - Bipolar “safety-pin” staining
 - Facultative intracellular pathogen



Plague: Epidemiology

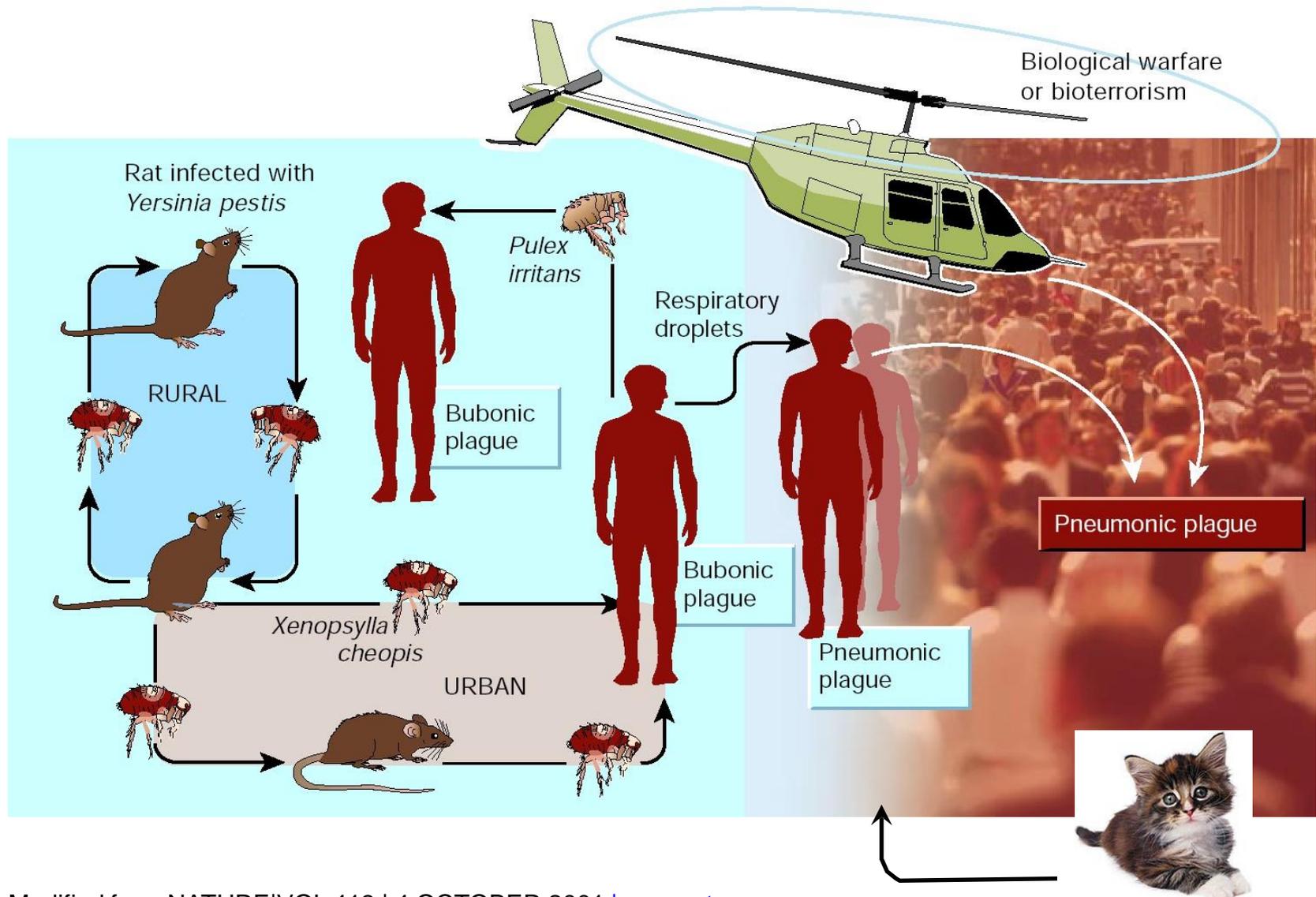
- Globally 1000-3000 cases reported annually
- Most cases reported in underdeveloped countries
- Case Fatality Rate: up to 70%

Figure 1 - Human plague cases : countries having notified to WHO, 2002-2005



Data Source: Epidemic Readiness and Interventions; Communicable Diseases (CDS); Map production: Public Health Mapping & GIS; Communicable Diseases); World Health Organization.

Plague: Transmission



Bubonic Plague (80-95% of cases)

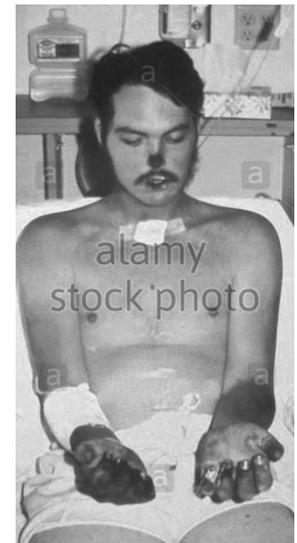
- Incubation 2-8 days (mode 3-5 days)
- Sudden onset of flu-like syndrome
 - Fever up to 40°C (104°F)
 - Malaise (75%), chills (40%), headache (20-85%), altered mentation (26-38%), N/V (25-49%)
 - Abdominal pain (50%)
- Bubo develops within 24 hours
 - Swollen, infected lymph node (1-10 cm size); v. painful, rarely suppurates
 - Femoral > inguinal > axillary, cervical
 - Any lymph nodes can be involved;
- Other findings
 - Papule, vesicle, eschar, or pustule = Flea bite (25%)
 - Tender palpable liver and/or spleen
 - Acute abdomen (intra-abdominal node buboes)



Mortality: 60% if untreated, <5% with prompt therapy

Septicemic Plague (10-20% cases)

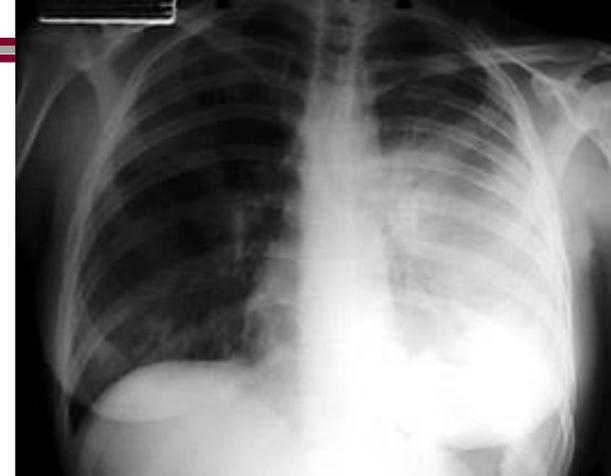
- Secondary extension of bubonic form
 - ~25% of all bubonic forms progress
 - High density bacteremia; rapid multiplication in blood
- Primary cases possible
 - Absence of lymphadenopathy and pneumonia
- Symptoms:
 - Gram negative septicemia
 - High fever, chills, prominent gastrointestinal (nausea, vomiting, diarrhea, abdominal pain)
 - Hypotension, tachycardia, tachypnea
 - Microvascular thrombosis in small, acral vessels (**DIC**: *Y. pestis* coagulase – plasminogen activator)
 - Purpura, necrosis, gangrene (“**black death**”)



Mortality: 100% if untreated, 30-50% with prompt therapy

Pneumonic Plague

- Primary (3-28%) or secondary (12%)
- Incub: 1-6 days (Mean: 2-3 days)
- Acute onset
 - fever, chills, malaise +/- lymphadenopathy
- Fulminant illness
 - Rapidly advancing tachypnea, dyspnea, hypoxia, chest pain, cough, hemoptysis
 - Purulent sputum – may become blood-tinged or grossly hemorrhagic
- CXR – non-specific
- GI symptoms are often present
- Death from respiratory failure and circulatory collapse



Mortality: 100% if untreated, 57% with prompt therapy

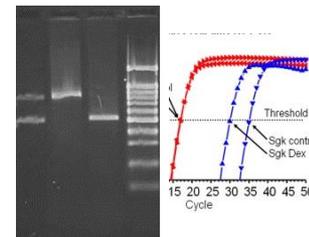
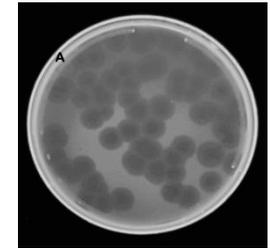
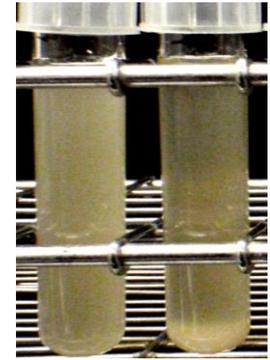
Rare Forms of Plague

- Pharyngeal
 - Results from ingestion or inhalation of *Y. pestis*
 - Sore throat, fever, malaise, headache, painful cervical lymph nodes
- Meningeal
 - Fever, headache, nuchal rigidity, seizures and all symptoms of severe meningitis
 - Buboes are common, esp. axillary buboes
- Cutaneous
 - Multiple pustules, ulcers, eschars, carbuncles, esp. at the site of flea bite



Plague: Diagnosis

- Clinical diagnosis – usually much easier than for brucellosis
- Diagnostic materials: lymph node needle aspirate, nasopharyngeal swabs, sputum, blood, CF samples
- Presumptive dx – microscopy, IF
- Definitive dx: culture isolation (BHI, HIB, blood agar, MacConkey agar) and identification (bacteriophage, serology, PCR). Usually takes 48-72 h, start therapy immediately!
- Testing patients' serum samples: F1, V antigen (agglutination, ELISA). Titers: $>1/10$ is suggestive, $>1/128$ is more specific, 4-fold rise in acute vs. convalescent is confirmatory
- PCR tests (both conventional and RT): down to 10 CFU/ml
- Our data – indirect phage-based *Y. pestis* detection: 1 live bacterium per 1- μ l sample from blood for 4 h, can be increased by sample concentration



Plague: Treatment

- Parenteral antibiotics recommended initially
 - Streptomycin (old favorite) 1gm IM bid, or
 - Gentamicin 5 mg/kg IV daily, or 2mg/kg loading dose then 1.7 mg/kg IM or IV q8h, or
 - Doxycycline 200 mg IV then 100mg q12h, or
 - Ciprofloxacin 400 mg IV q12h
- Switch to oral antibiotics after appropriate clinical improvement
- Duration of Rx: 10-14 days
- Meningitis, drug of choice – chloramphenicol
- **Drug-resistant strains!**



Plague: Prevention

- Infection Control: Standard precautions PLUS:
 - Suspect pneumonic: Droplet precautions until pneumonia ruled out or until 48-72 hrs of appropriate antibiotics
 - Confirmed pneumonic: Droplet precautions until sputum cultures negative

MMWR 1996;45:RR-14



- Post-exposure Prophylaxis:

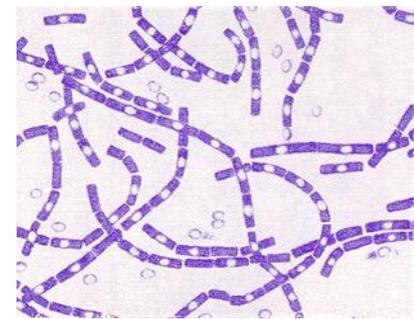
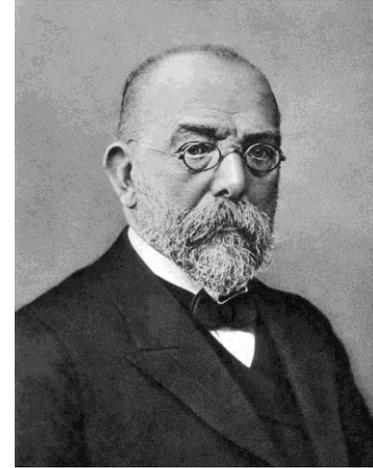
Indication	Duration	Antibiotic
Face to face contacts (≤ 2 meters) of pneumonic case	7 days	Preferred: Doxycycline 100 mg orally BID Alternatives: Ciprofloxacin 500mg orally BID Chloramphenicol 25mg/kg orally QID
Suspected exposure to plague aerosol	Duration of exposure plus 7 days	Others: Other tetracyclines, fluoroquinolones TMP/SMX if susceptibility tests allow



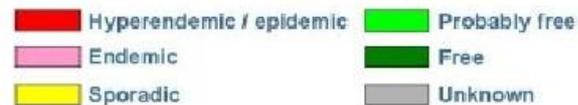
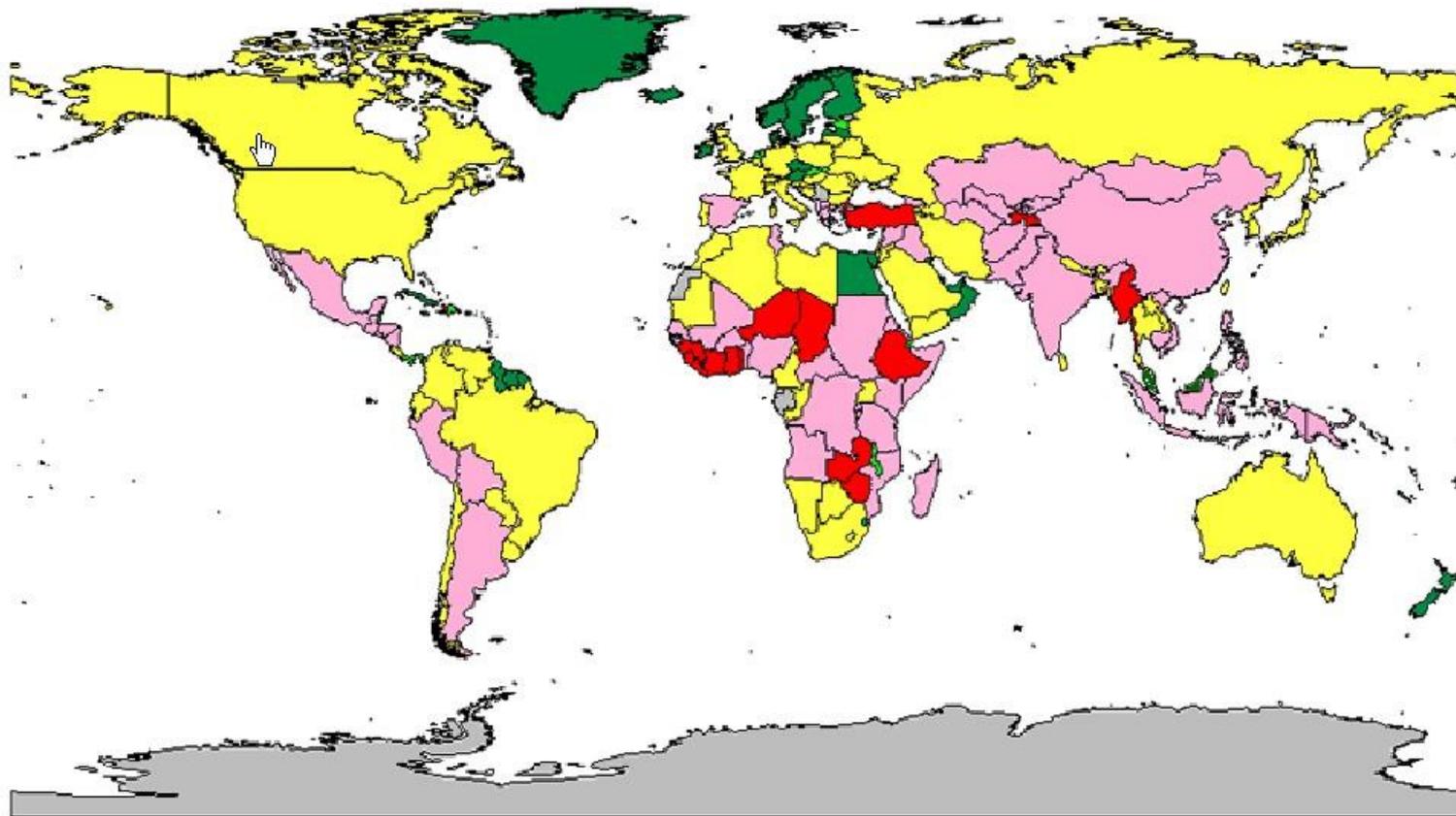
- Vaccines: Not FDA approved. IND vaccine candidates composed of *Y. pestis* F1 and V antigen developed

Anthrax: Introduction

- Anthrax/*Bacillus anthracis*: from Greek for coal, anthrakis
- First clinical descriptions for animals and humans in 18th century; first disease for which microbial cause was defined (Robert Koch)
- Primarily disease of herbivores; hardy spore persists in soil reservoir
- Humans usually infected (naturally) by contact with infected animals or contaminated animal products
- In U.S.:
 - ~130 cases/yr in early 1900s (Woolsorter's disease)
 - Before the 2001 "Amerithrax" attacks, 18 cases of inhalational anthrax reported in the 20th century
 - Last naturally-occurring inhalation case in 1976; cut. 2-5/year
- The cause, *Bacillus anthracis*, Gram-positive spore-forming bacterium, easily cultivated & stabilized, thus easily weaponized



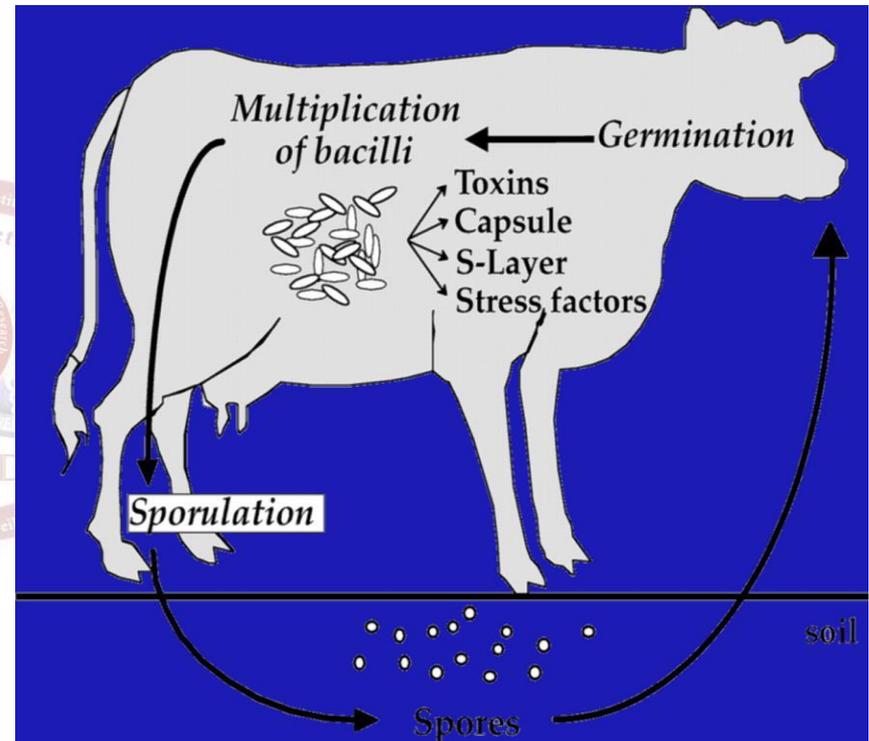
Anthrax: Epidemiology



Source: www.infectionlandscapes.org

Anthrax: Transmission

- Spores are the infective form
- *B. anthracis* bacilli (vegetative cells) are shed by the dying animal and sporulate on contact with O₂, resulting in soil contamination.
- 2,000-5,000 human cases/yr
- **Risk Groups:**
 - Farmers, ranchers/shepherds
 - Wool mill workers
 - Tannery, bone meal workers
 - Drum makers (natural hide) or players
 - Laboratory workers
 - Military personnel



Anthrax life cycle

Anthrax Case Definition

- Acute onset, distinct clinical forms:
 - Cutaneous: skin lesion evolving in 2-6 days from a papule, through a vesicular stage, to a depressed black eschar
 - Inhalational*: brief prodrome resembling a viral respiratory illness, followed by development of hypoxia and dyspnea, with radiographic evidence of mediastinal widening
 - Intestinal: severe abdominal distress followed by a fever and signs of septicemia
 - Oropharyngeal: mucosal lesion in oral cavity or oropharynx, cervical adenopathy & edema, fever

*Presentation may vary in the context of bioterrorism

[MMWR 1997;46\(RR-10\)](#)

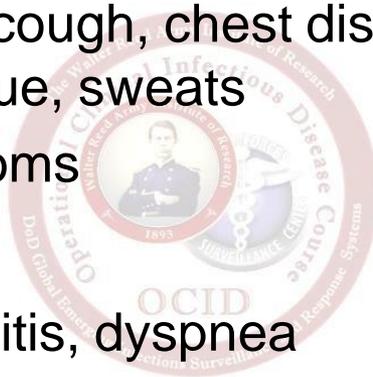
Cutaneous Anthrax

- Most common form (95%) under natural conditions
- Portal of entry: break in skin
- Incubation: hours - 12 days
- Papule → vesicle → ulcer/painless eschar
- Significant edema surrounding the lesion, and in nearby lymph nodes
- Fever, malaise, headache may be present
- Death 20% untreated; rare if treated

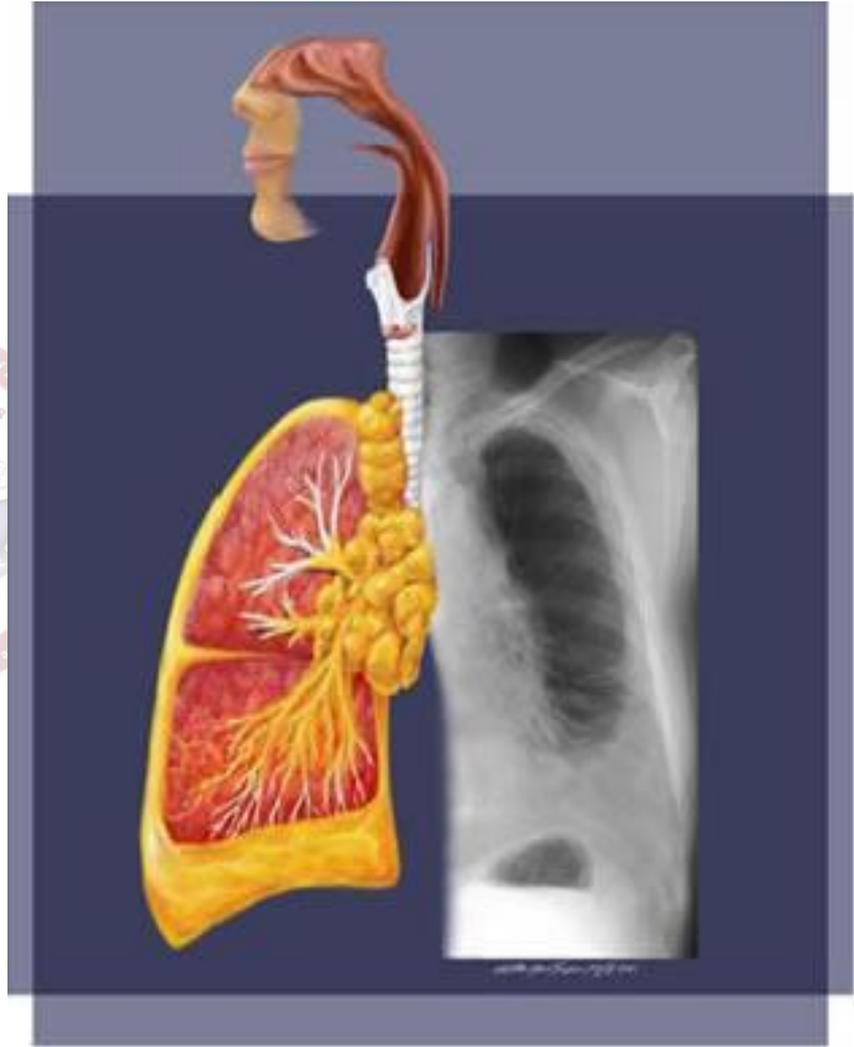
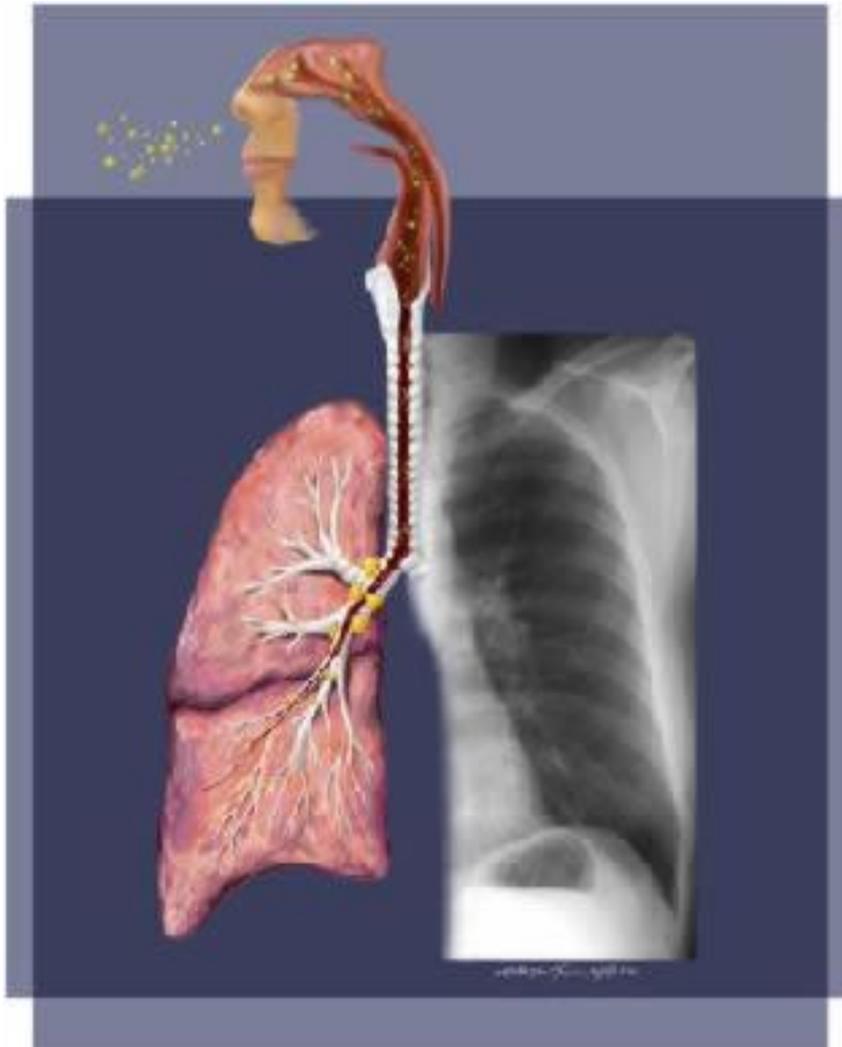


Inhalational Anthrax

- Incubation period: 1 to 43 days or longer; may be related to dose and host factors
- Initial symptoms typically appear in 2-5 days
 - Nonspecific: fever, dry cough, chest discomfort, muscle aches, malaise, profound fatigue, sweats
 - Gastrointestinal symptoms
- Late symptoms
 - Hemorrhagic mediastinitis, dyspnea
 - Some cases develop meningitis
 - Rapid progression to shock, death
- Mortality rate 100% despite aggressive Rx in “advanced disease” but is lower with early treatment; 6/11 cases in the 2001 outbreak survived with early aggressive therapy



Inhalational Anthrax



Gastrointestinal Anthrax

- RARE, naturally-occurring disease
- Ingestion of insufficiently cooked, contaminated meat (vegetative bacilli?)
- Probably requires a large inoculum of organisms
- Incubation period 1-6 days
- Symptoms- nausea, vomiting, fever, abdominal pain -> hematemesis, bloody diarrhea or melena and massive serosanguinous ascites
- Pathology- ulcerative lesions of terminal ileum, cecum, with hemorrhagic mesenteric adenopathy
- Hematogenous spread via direct extension from GI lumen leading to bacteremia and septicemia
- Mortality~50%

Anthrax: Diagnosis

- Isolation of *B. anthracis* from a clinical specimen
 - Blood, lung fluid, spinal fluid, skin lesion **OR**
- Positive serology* (after symptom onset) **OR**
- Demonstration of *B. anthracis* in a clinical specimen by immunofluorescence (DFA for cell wall and capsule)*
- Nasal swabs & serology – not useful for clinicians, but can help determine the extent of exposure in an epidemiologic investigation

*testing at state public health labs or CDC

[MMWR 1997;46\(RR-10\)](#)

Cutaneous Anthrax: Treatment (without systemic symptoms)

CFR – 20% untreated; <5% treated

1. PO Antibiotics (adult doses)

1. Natural exposure:

- 7-10 days PO antibiotics

2. Associated with potential BW aerosol attack:

- Ciprofloxacin 500mg PO q12hr for 60 days, or
- Doxycycline 100mg PO q12hr for 60 days*

2. NSAIDS/Steroids for severe edema?

3. Infection control:

- Contact precautions
- Do not debride lesions

*Until susceptibilities known.

-May switch to Amoxicillin po

-Avoid DOXY in pregnancy and in children <8yr

Inhalational Anthrax: Treatment

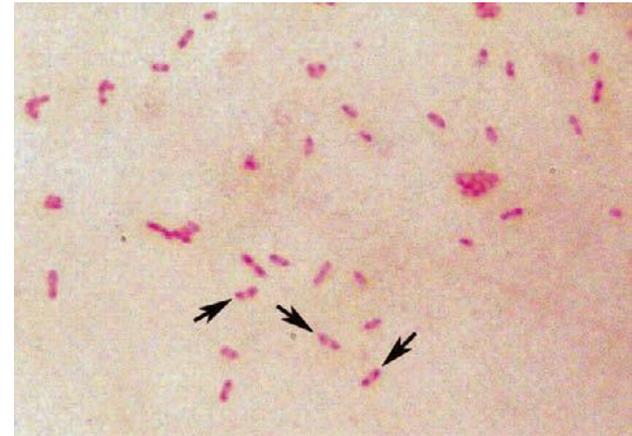
- Ciprofloxacin or doxycycline
 - Fluroquinolones with similar activity and CNS penetration preferred over doxycycline
- One or two additional antimicrobials with adequate CNS penetration and expected *in vitro* activity
 - e.g. rifampin, vancomycin, penicillin, ampicillin, meropenem
- Clindamycin recommended due to ability to inhibit protein synthesis
- 60 day course
- Switch to single PO med upon improvement
- May have to use PO antibiotics in mass casualty situation
 - Avoid Doxy in pregnancy, children under 8yr old
 - Same antibiotic regimen for **GI anthrax** or **septic cutaneous anthrax**

Anthrax: Prevention

- Infection Control:
 - Standard precaution for inhalational anthrax - not transmissible person to person
 - Cutaneous anthrax RARELY transmitted - some recommend contact precautions
 - 0.5% hypochlorite solution for cleaning
- Postexposure prophylaxis (CDC recommends):
 - 60 days of oral antibiotics (Ciprofloxacin, Doxycycline, Procaine Penicillin G and Levofloxacin) +
 - 3 doses of anthrax vaccine adsorbed (AVA) at 0, 2 and 4 weeks (IND protocol or an Emergency Use Authorization)
- First effective bacterial vaccine in 1881 (Pasteur and Greenfield)
- Vaccine: Anthrax Vaccine Adsorbed (AVA-Biothrax)
 - Licensed by Food and Drug Administration (FDA) since 1970
 - AVA now given IM at 0 and 4 weeks and 6, 12, and 18 months

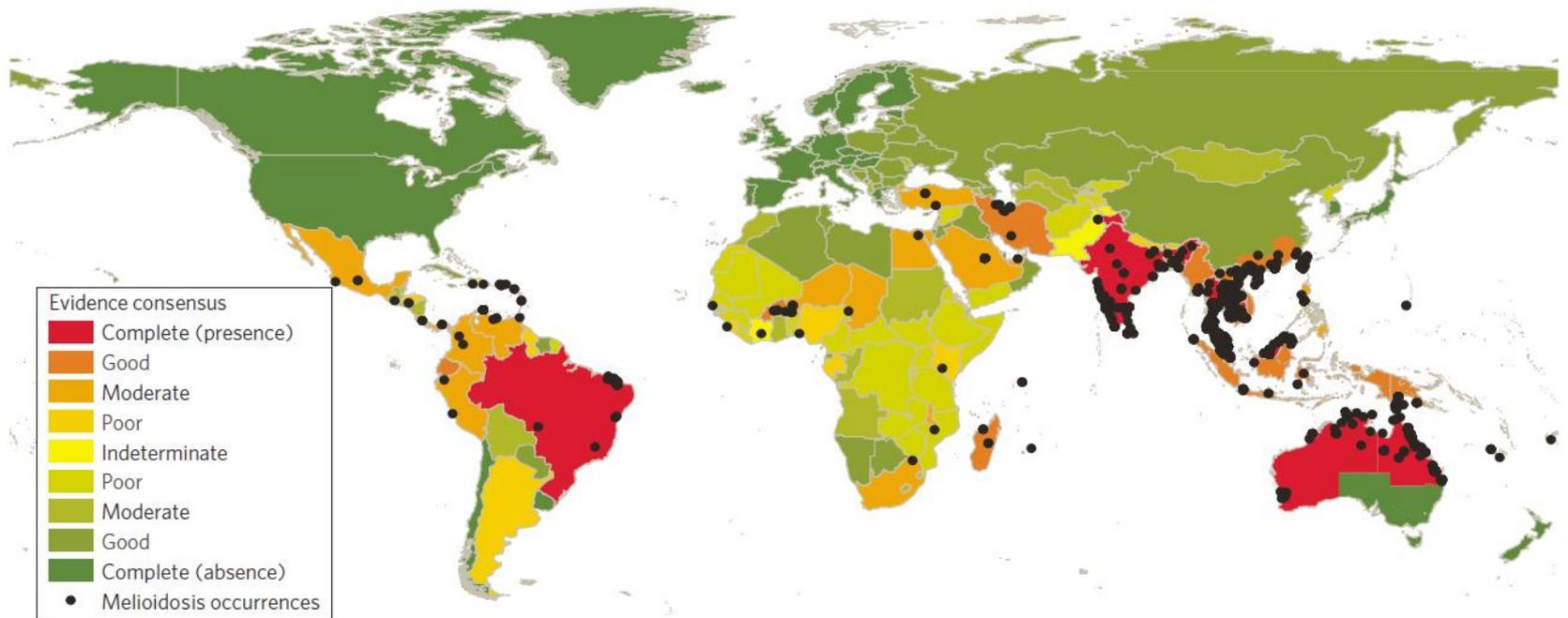
Melioidosis: Introduction

- Emerging tropical potentially fatal disease
- Septicemia and pneumonia
- Systemic and localized
- Acute subacute, chronic
- Many asymptomatic infections
- Diabetes is predisposing condition
- The number of cases is growing
- Geography is expanding
- *Burkholderia pseudomallei*
 - Gram-negative saprophyte
 - Bipolar staining, “safety pins”, similar to *Y. pestis*
 - High concentrations in soil, water
 - Intrinsically MDR
 - On plates looks similar to *Pseudomonas* and thus often neglected



Melioidosis: Epidemiology

- Globally 165,000 cases of human melioidosis annually
- 89,000 (53.9%) people die
- Most cases reported in South and East Asia, Pacific, Sub-Saharan Africa and Australia



Source: Limmathurotsakul *et al.* 2016. Predicted global distribution of *Burkholderia pseudomallei* and burden of melioidosis. *Nat. Microbiol.* Epub. Online 11 January.

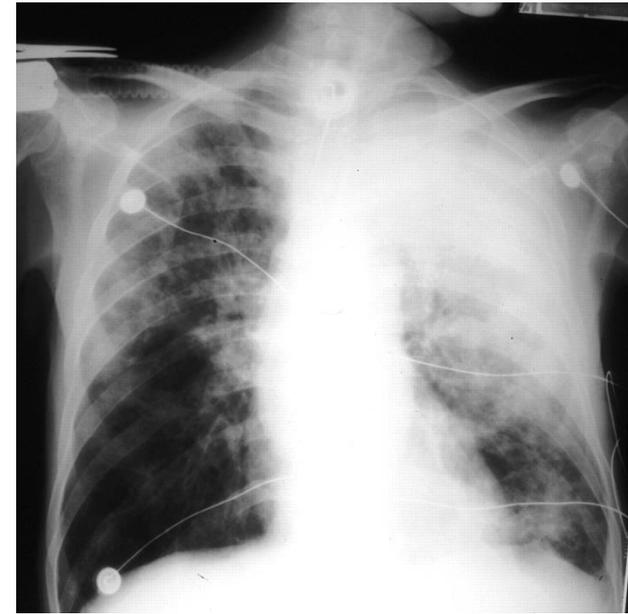
Melioidosis: Transmission

- Wound infection
 - Direct contact with contaminated soil or water
- Ingestion
 - Contaminated water
- Inhalation
 - Dust in endemic areas
- Rarely:
 - Person-to-person
 - Animal-to-person



Pulmonary Melioidosis

- 50-80% cases
- Incubation period: mean 9 days, most often 1-21 days, but considered to be as long as 62 years(!)
- Primary or secondary
- Cough, fever, night sweats, headache
- Lobar pneumonia or segmental consolidation
- Predilection for the upper lobes
- Primary lung abscesses are possible
- Cavitation is common
- Sputum is often purulent
- Hemoptysis may be present
- Often dissemination:
 - Cutaneous abscesses (10-20%)
 - Liver and spleen abscesses
 - Prostatic abscesses (2-15%)



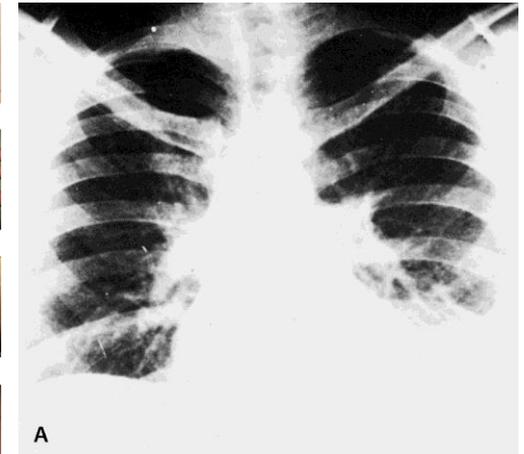
Mortality: 50% in Thailand, 19% in Australia

Septicemic Melioidosis

- Fever, rigors, night sweats
- Myalgia, anorexia, headache
- Regional adenopathy, lymphangitis
- Papular or pustular skin lesions
- Diarrhea, hepatosplenomegaly
- Bacteremia (up to 60%)
- Abscesses
 - Cutaneous abscesses
 - Liver and spleen abscesses
 - Prostatic abscesses
 - Multi-organ abscesses
- Secondary pneumonia



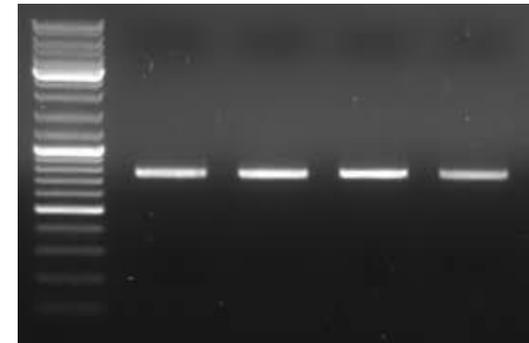
Liver abscess



A
Splenic abscess – left hemidiaphragm elevation

Melioidosis: Diagnosis

- Clinical diagnosis:
 - Blood tests: leukocytosis with a shift to the left
 - Radiographic studies
- Diagnostic materials: sputum, blood, abscesses, wounds, urine
- Presumptive dx – microscopy, IF
- Culture method (from non-sterile sites – Ashdown's selective medium: crystal violet + Gm; 37.5°C). Primary isolation takes 48-72 h
- PCR, immunoassays for confirmation
- Serology: agglutination, ELISA. Single IgM titer $>1/160$ or 4-fold titer increase suggest active infection



Melioidosis: Treatment

- Severe disease:
 - Ceftazidime (120 mg/kg/day IV in 3 divided doses)
 - Imipenem (60 mg/kg/day IV in 4 divided doses, max 4g/day)
 - Many experts add TMP/SMX (TMP 8 mg/kg/day IV in 4 divided doses)
 - IV antibiotics for ≥ 14 days
- Median time for fever resolution is 9 days
- After that, oral antibiotic maintenance for at least 20 weeks
- Longer courses (6-12 months may be required)

Melioidosis: Prevention

- Avoid contact with contaminated soil or water in endemic areas
- Persons with open skin wounds and those with diabetes or chronic renal disease should be particularly careful
- Agricultural workers should wear solid boots to prevent infection through the feet and lower legs
- Health care workers can use standard contact precautions (mask, gloves, and gown) to help prevent infection
- No vaccine available for human use
- Postexposure chemoprophylaxis:
 - TMP-SMX or Doxycycline or Ciprofloxacin
 - Duration – at least 10 days

Case Study

- 35 yo female
- Co-worker opened a letter containing white powder a week earlier.
- The powder was checked by the FBI for anthrax and was negative.
- She has a poorly healing lesion on her shoulder now.
- She has seen multiple physicians without a diagnosis.



Case Study (cont.)



Case Study: Ddx on Black Eschar

- Brown Recluse Spider bite
- Bacterial:
 - Anthrax
 - Tularemia
 - Plague
 - Cutaneous diphtheria
 - Ecthyma gangrenosum
- Viral: Orf
- Fungal:
 - Sporotrichosis
 - Aspergillus
 - Mucor
- Parasitic: cutaneous leishmaniasis
- Mycobacterial: TB and non-TB
- Rickettsiae
- Non-infectious: coumarin necrosis

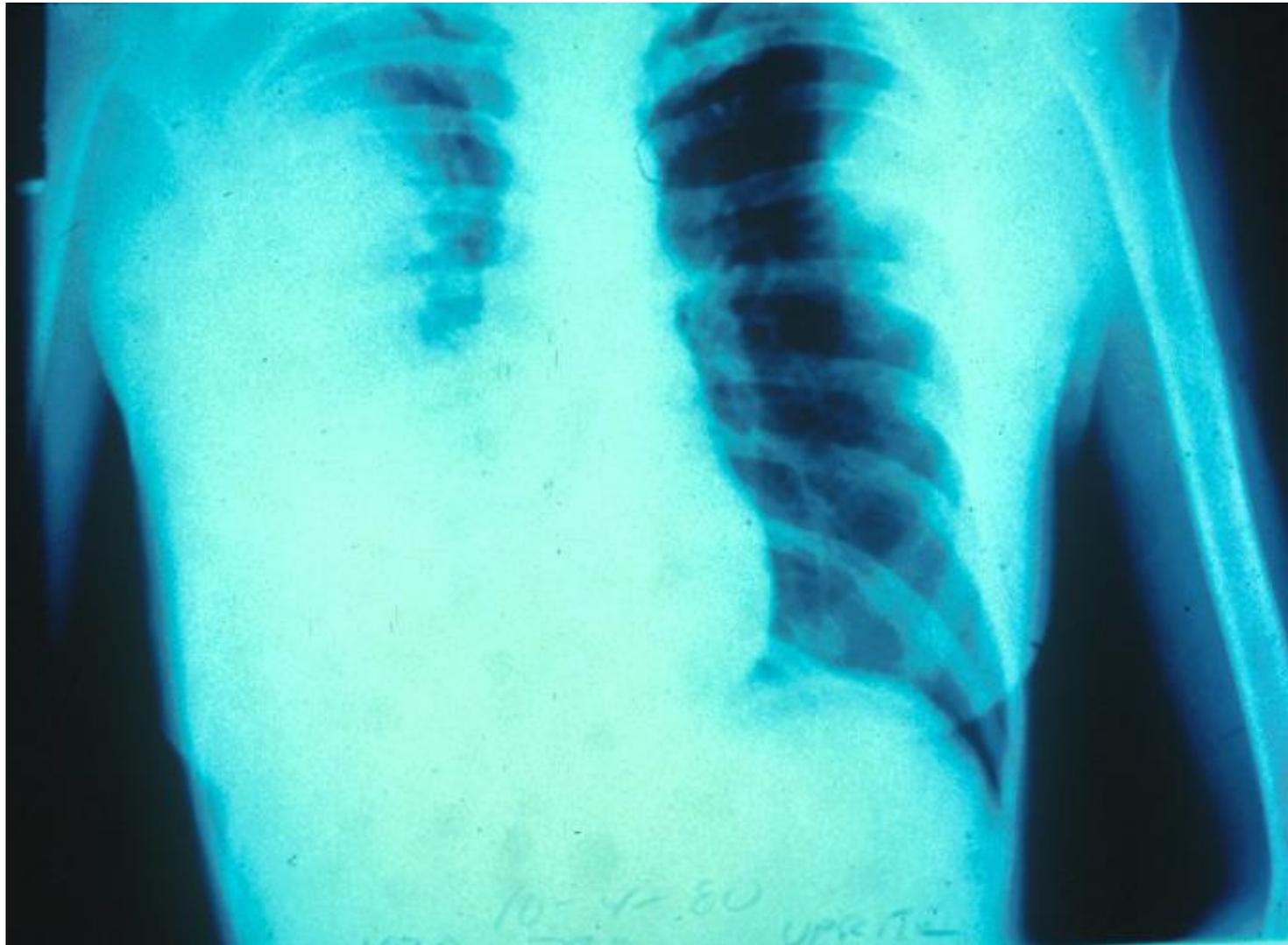


Case Study (cont.)

- Day 3, new symptoms:
 - high fever (104°F)
 - shaking chills
 - headache
 - cough
 - dyspnea
 - myalgias

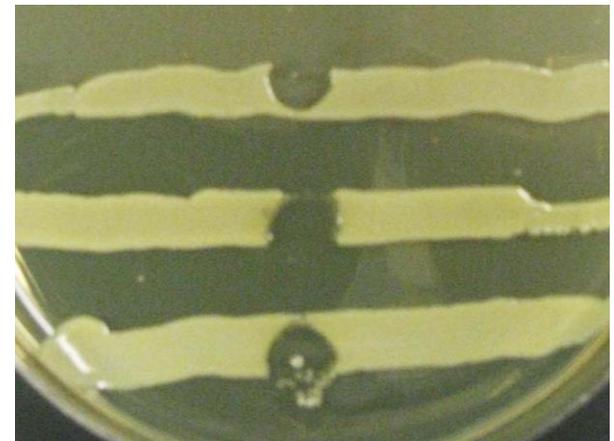
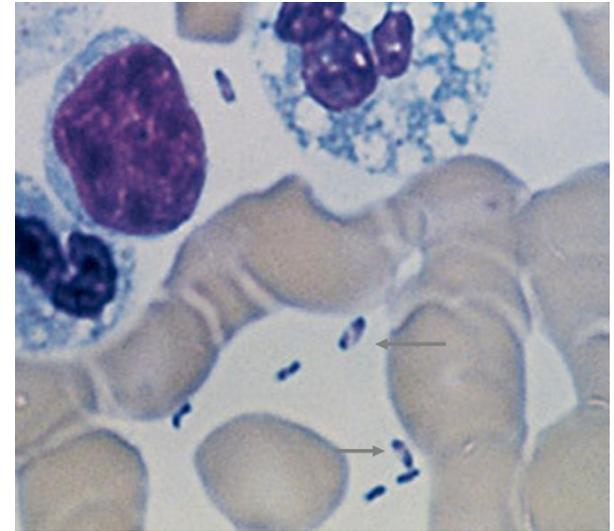


Case Study, cont. (CXR)



Case Study (cont.)

- Blood smear: bipolar-staining rods
- Sputum smear: bipolar-staining rods
- Blood culture in BHI: agglutinative growth in 16 h
- Grey-white translucent colonies on Blood agar in 24 h
- Positive test with plague diagnostic bacteriophage
- ELISA with anti-F1 Mab: positive
- Dx: Cutaneous/pneumonic plague!



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Summary

- Biothreat infections are endemic for many tropical countries
- Many biothreat infections are travelers' diseases
- There are a number of epidemiologic clues of a BW or terrorist attack
- Rapid diagnosis is particularly important for biothreat infections
- Prompt antibacterial therapy is paramount even before definitive dx
- Alternative therapies are needed due to MDR strains
- There are only few FDA-approved vaccines; more vaccines should be developed

Questions?
