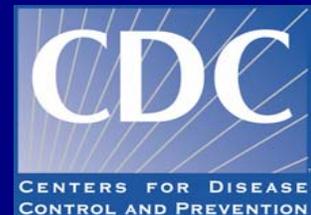


# Anthrax

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# Overview

- History, etiology, pathogenesis
- Burden of natural disease
- Disease forms
- Recognition and diagnosis
- Differential diagnosis
- Treatment
- Prevention

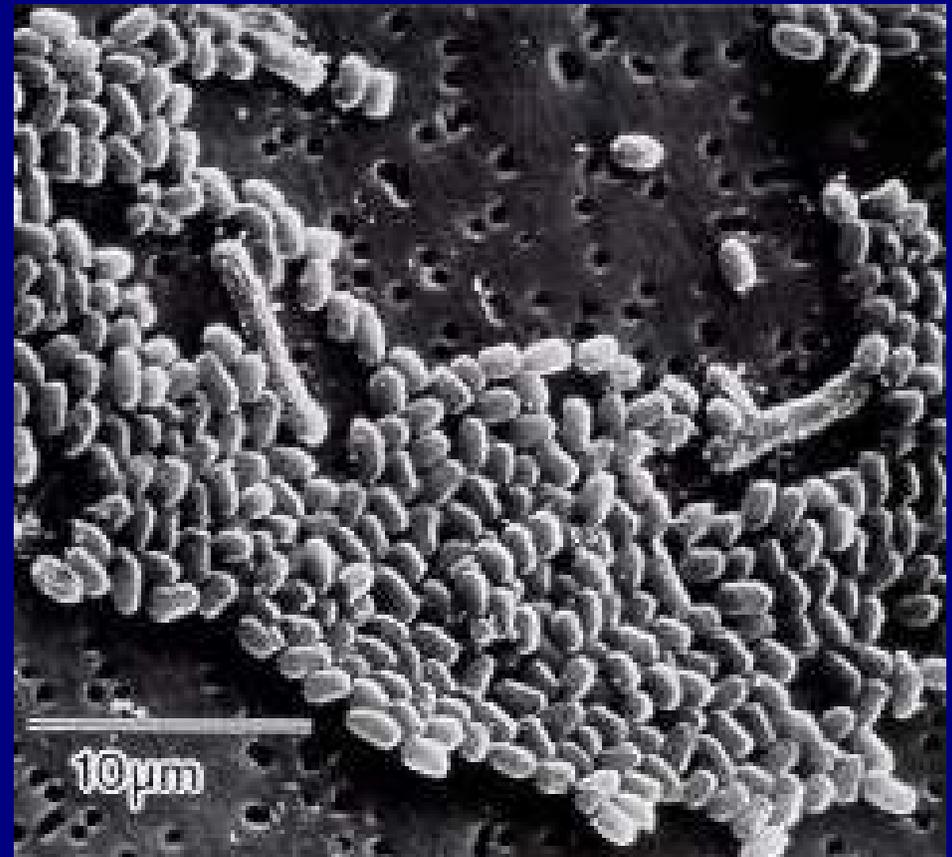
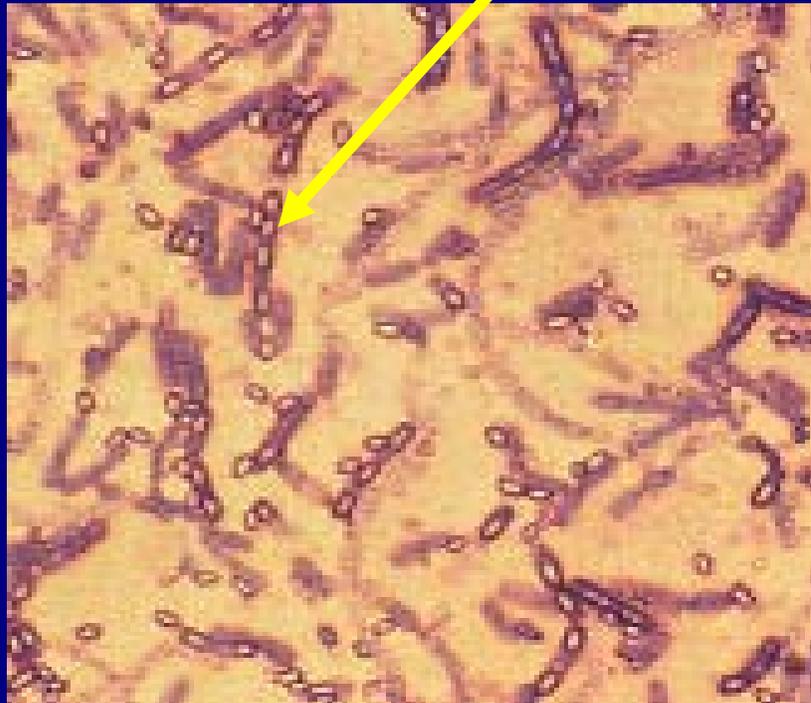
# History

- **Malignant Pustule, Malignant Edema, Siberian plague, Black Baine, Ragpicker's disease, Woolsorter's disease**
- **Described since ancient times**
- **Medieval Period - multiple pandemics**
- **1876 - The first microbial etiology (Koch)**
- **1881 - The first live bacterial vaccine (Pasteur)**

# Etiology

- *Bacillus anthracis*

- Gram positive, spore forming, non-motile bacillus

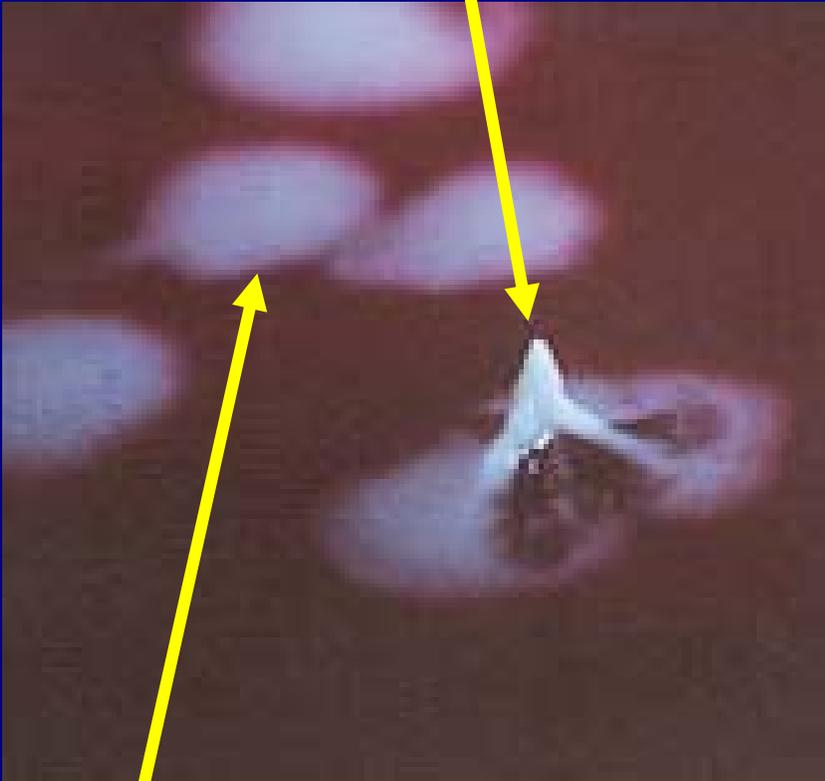


# *Bacillus anthracis*: Microbiology

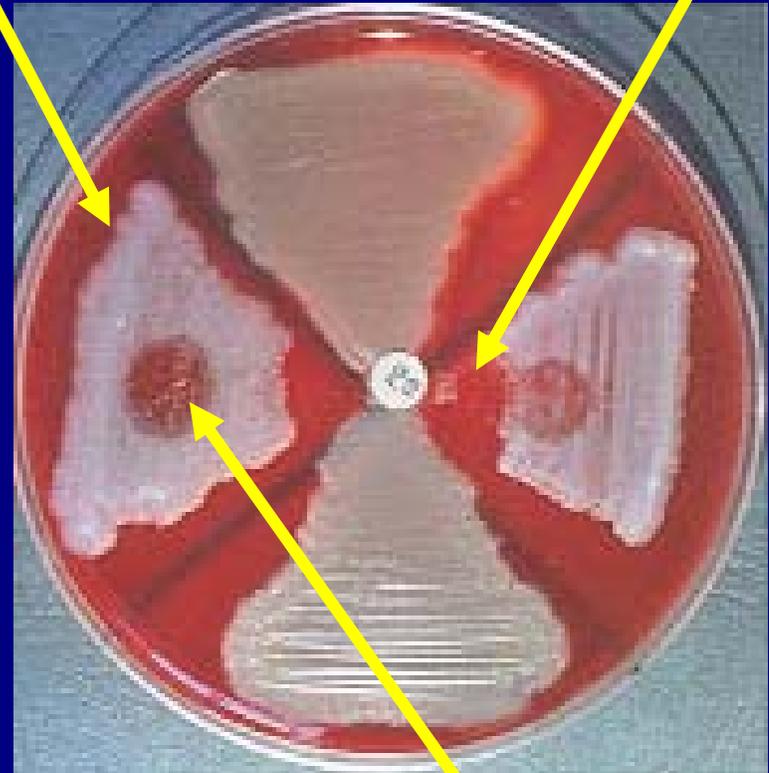
Tacky (egg white)

Non-hemolytic

Penicillin susceptible (97%)



Tails (medusa head) colony morphology



Phage susceptible

# Anthrax Binary Toxins

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**Lethal Factor**

**(LF, 90kDa)**

Endopeptidase

**Protective Antigen**

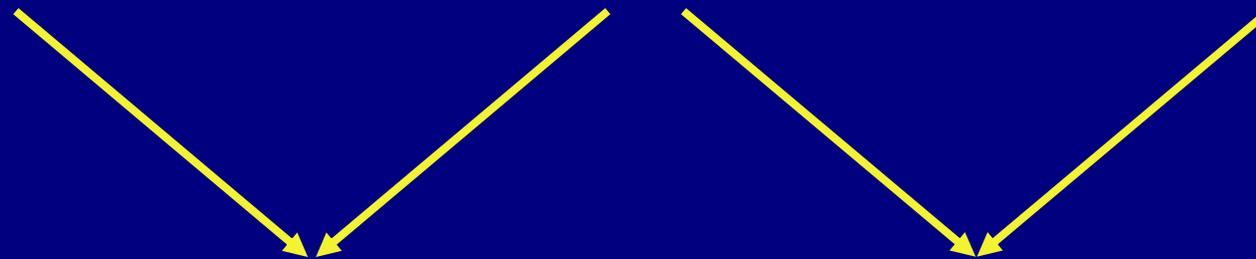
**(PA, 83kDa)**

Receptor binding & toxin internalisation

**Edema Factor**

**(EF, 89kDa)**

Adenylyl cyclase



**Lethal Toxin**

**Edema Toxin**



**MAPKK cleavage**

**ATP -->cAMP**

**MØ lysis**

**Cytokine modulation**

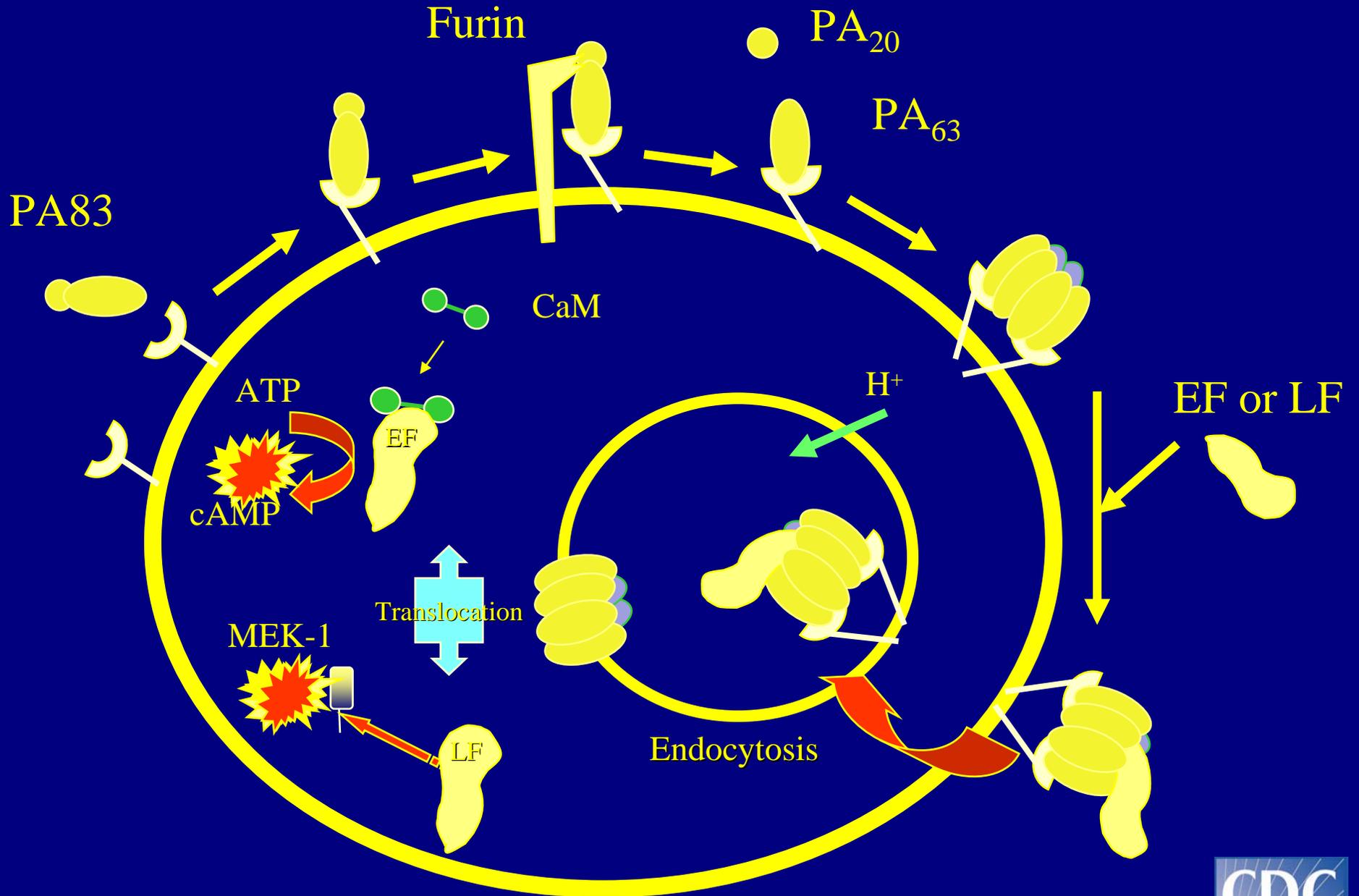
**Cytokine modulation**

**Edema**

**Fatal toxic shock**

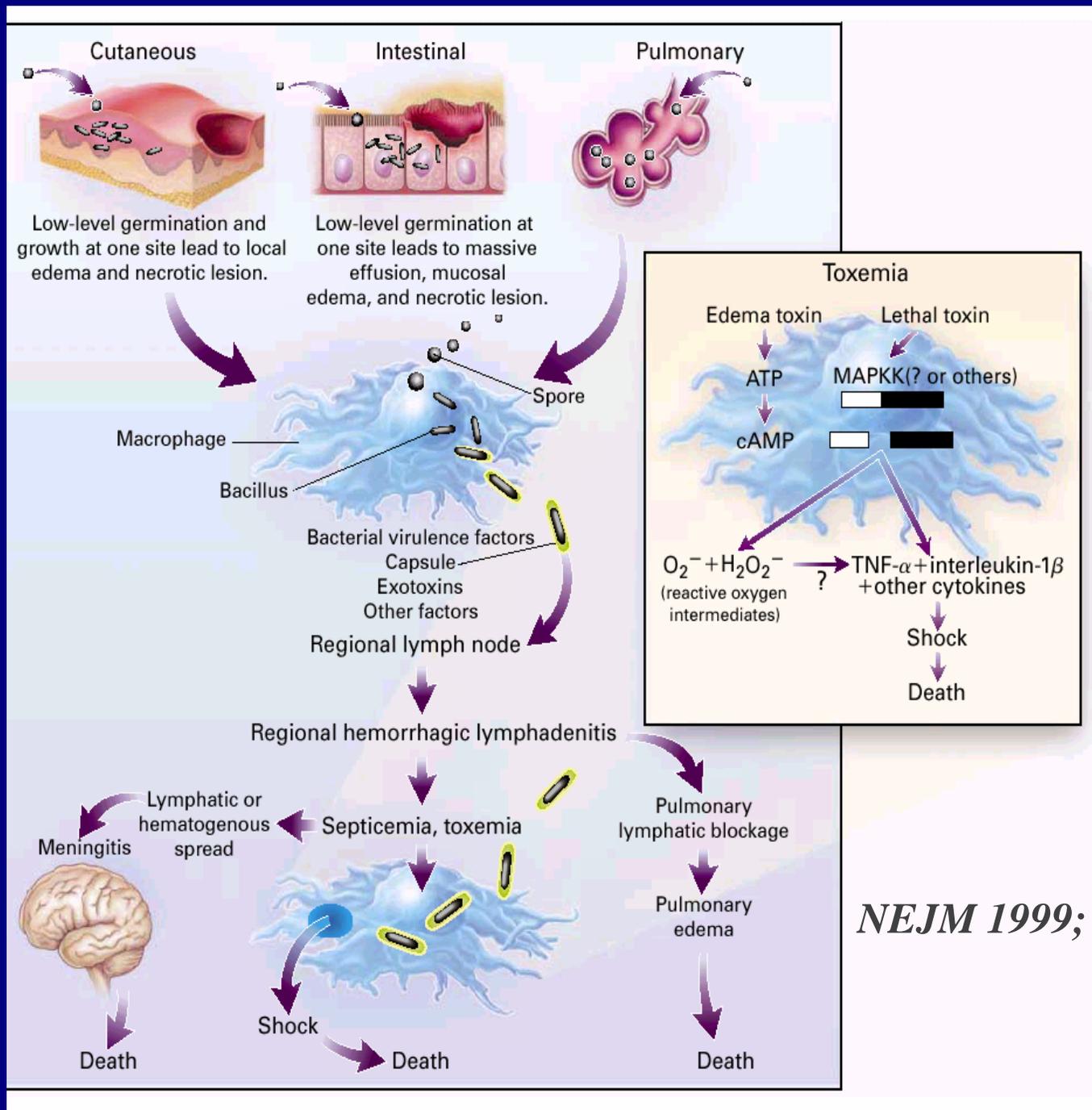
# Anthrax Toxin - Mode of Action

(from Leppla, 1999)



# Pathogenesis of Anthrax

## Spores



*NEJM 1999; 341: 815- 826*

# Anthrax in Animals

Rapid progression from febrile illness to death with hemorrhage



Dogs and pigs get a pharyngeal form – more resistant

# Epidemiology and Transmission in Humans

Spores live in the soil for many yrs: at least 60 yrs

Animals ingest spores

Humans become infected from animal products

- Cutaneous: direct contact
- Gastrointestinal: ingestion of infected meat
- Inhalation: inhalation of aerosolized spores

Generally, not transmissible person-to-person

# Why is Anthrax a Threat Agent?

- Persistence of endospore in environment
- Pathogenicity
- Delayed onset of recognizable symptoms renders treatment ineffective
- Can be manufactured using standard laboratory equipment
- No recognizable color, taste, or odor

# 2001 Anthrax Threat Letters



# Examples of Sources

- **Animals with anthrax - veterinarians**
- **Contaminated hair, hides - mill workers, hobbyists**
- **Contaminated meat (not in milk) - Africa**
- **Biological warfare-related - 1979 Sverdlosk, Russia**
- **Bioterrorism-related – US anthrax letters, 2001**

# Burden of Natural Disease

- Disease absent/sporadic in Northern Europe
- More common in Greece, Italy, Spain, Turkey, Yugoslavia
- U.S. - South Dakota, Nebraska, Oklahoma, Texas
- Endemic in Central America, Peru, Bolivia, Venezuela
- Hyperendemic in Middle Eastern and adjoining countries of former USSR republics
  
- Largest recent epidemic: Zimbabwe, 1978-80 - 10,000 human cases
  
- Reporting deficiencies due to decreasing veterinary experience in case recognition and civil unrest

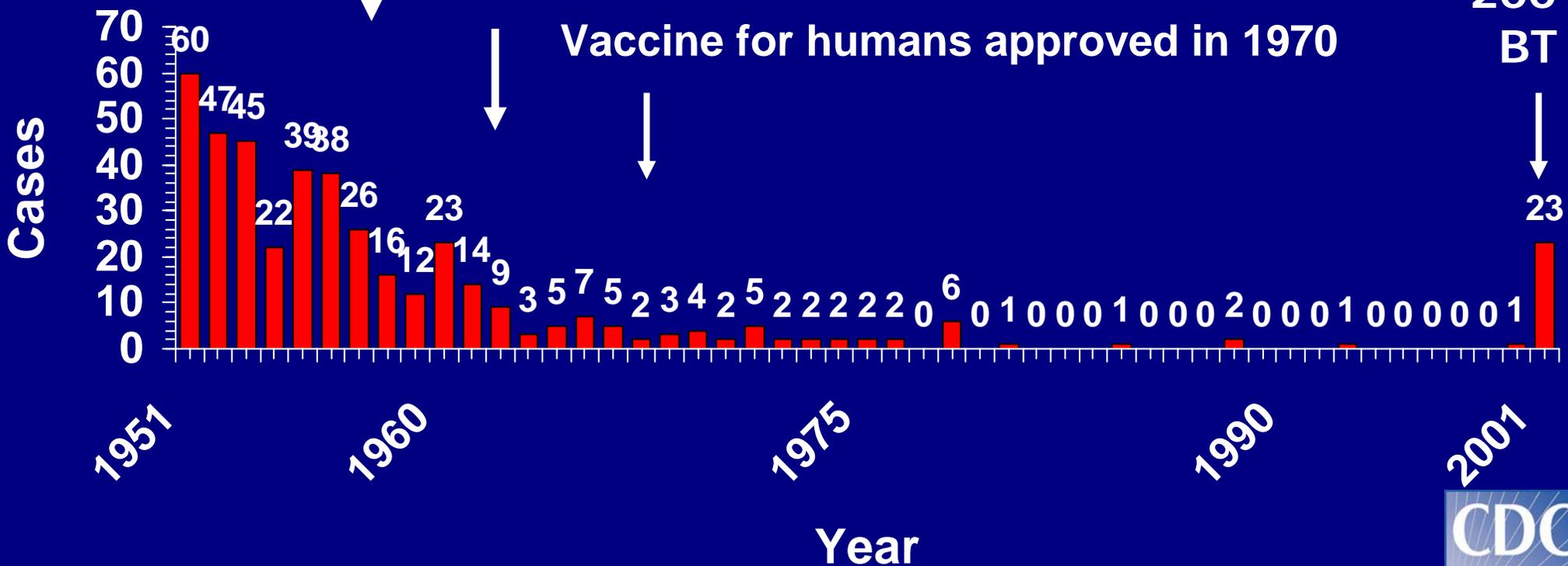
# Cases of Anthrax in the United States 1951-2001

Animal (Sterne strain) vaccine started in 1957, after Oklahoma enzootic; recommended in endemic areas thereafter

Formalin treatment of imported hides

Vaccine for humans approved in 1970

2001  
BT



# Cutaneous Anthrax

- 95% of human cases
- 1 - 2 days post exposure, papule develops (2 - 19 days)
- 2 - 4 days, ulcer surrounded by vesicles
- Black eschar forms - painless with edema
- Most common site is head, forearm, hands
- Untreated: 5-20% case-fatality rate

# Anthrax: Cutaneous

Vesicle  
development  
Day 2



Day 4



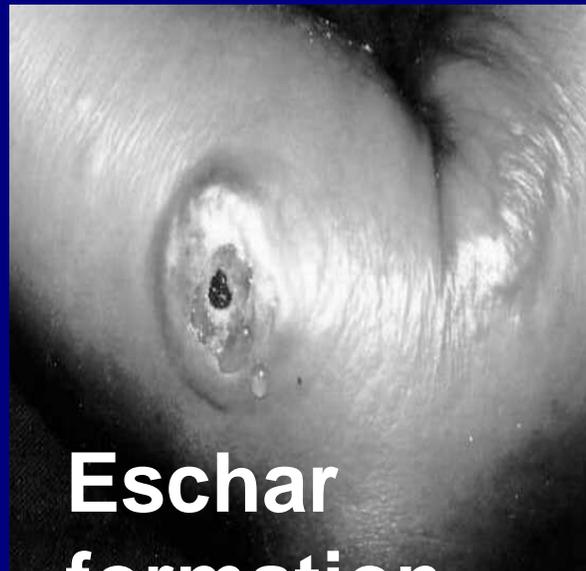
Day 6



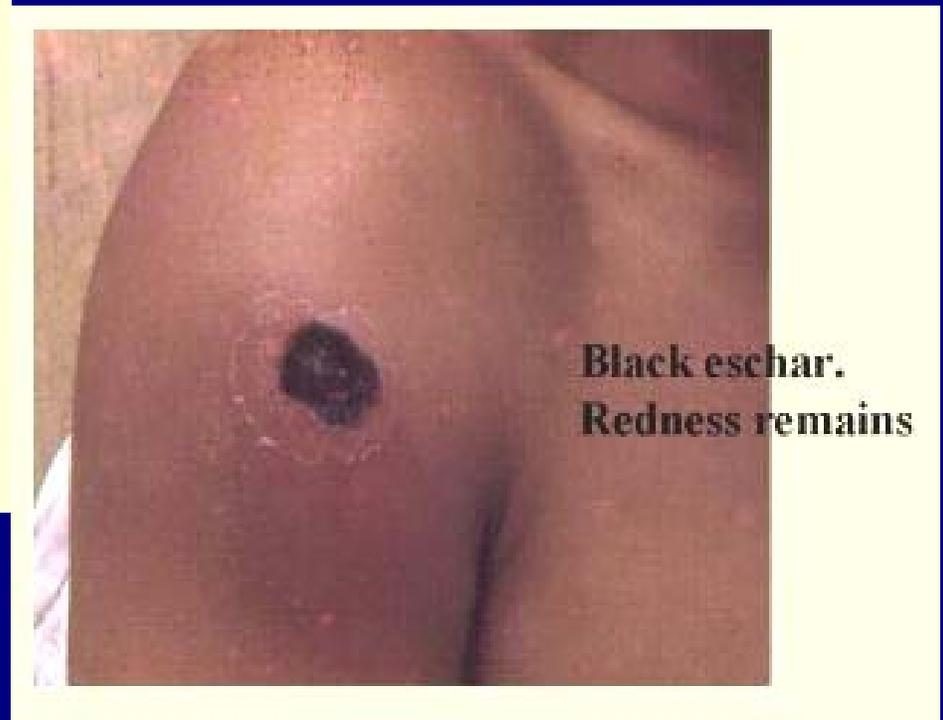
Day 10



Eschar  
formation



# Anthrax: Cutaneous



# Cutaneous Anthrax Resulting from Bioterrorism, NYC, October, 2001



# Diagnosis of Cutaneous Anthrax

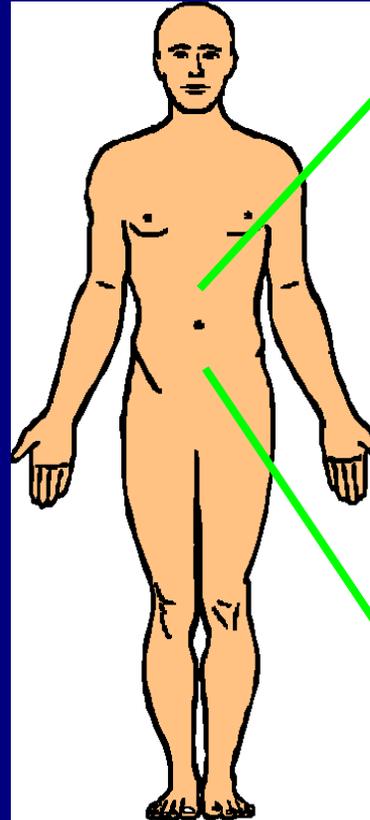
- Eschar formation
- Culture of vesicular fluid or exudate
- Blood culture
- Biopsy
- Polymerase chain reaction
- Immunofluorescence and immunohistochemistry

# Differential Diagnosis of Cutaneous Anthrax

- Spider bite
- Rickettsialpox
- Varicella zoster
- Herpes simplex
- Staphylococcal or streptococcal cellulitis
- Ecthyma gangrenosum
- Ulceroglandular tularemia
- Plague

# Gastrointestinal Anthrax

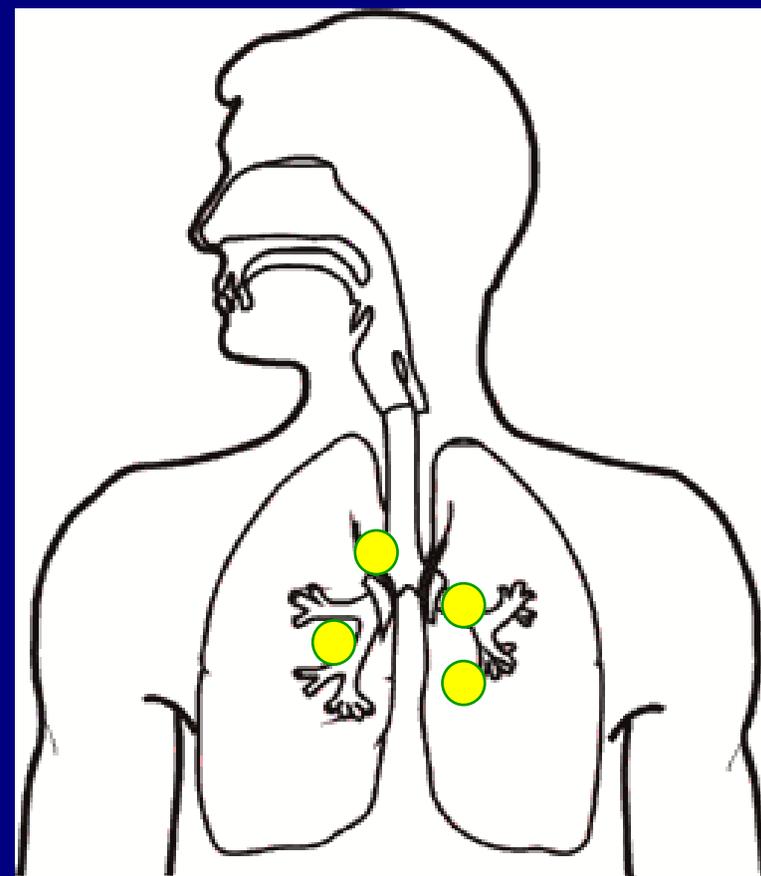
- Ingestion
  - Rare natural incidence
    - Undercooked, ground beef
  - Most simple, high-consequence application method
    - Possible route of choice for criminals and non-state sponsored terrorists
  - Symptoms
    - Nausea 2-5 days after ingestion
  - Mortality
    - Up to 50% without treatment



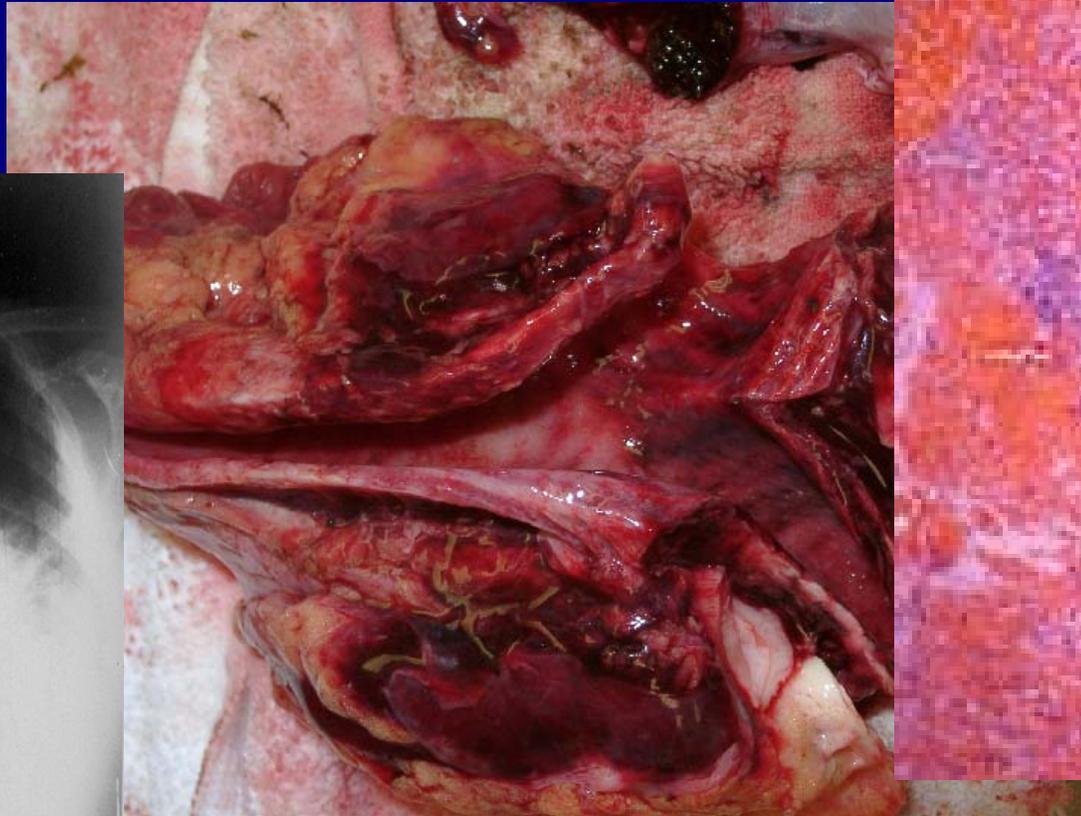
Intestinal lesion  
of GI anthrax

# Inhalation Anthrax

- Inhalation of spores
- Incubation, 2-3 days (range up to 60 days)
- Spores engulfed by macrophages and transported to mediastinal and peribronchial lymph nodes
- Insidious onset: malaise, low grade fever, nonproductive cough
- Abrupt development of respiratory distress
- Hemorrhagic mediastinitis
- Hematogenous spread
- Meningitis in 50%
- Case fatality rate before 2001 – 90%



# Inhalation Anthrax



# Inhalation Anthrax: Diagnosis

- Chest radiographs - widened mediastinum, pleural effusions
- Blood or cerebrospinal fluid culture and Gram stain
- Polymerase chain reaction (PCR)
- Immunofluorescence and immunohistochemistry

# Differential Diagnosis of Inhalation Anthrax

- Mycoplasmal pneumonia
- Legionnaires' disease
- Psittacosis
- Tularemia
- Q fever
- Viral pneumonia
- Histoplasmosis (fibrous mediastinitis)
- Coccidioidomycosis

# Distinguishing Anthrax from Influenza-like Illness (ILI)

- **ILI:**
  - Nasal congestion and rhinorrhea
  - ILI not usually associated with radiographic findings of pneumonia
  - Person-to-person spread
  - Rapid influenza testing and viral culture useful to indicate whether viruses are circulating among specific populations
- **Anthrax:**
  - Abnormal chest radiographs
  - No person-to-person spread

# Treatment of Inhalation or Complicated Cutaneous Anthrax

## Assumptions:

- Rapid progression / systemic
- Beta-lactamases were present in isolates from FL, NY, DC (2001)
- Toxin – mediated
- High fatality

## Strategy:

- Early treatment
- Combination therapy
- Avoid penicillins, at least early
- ? Antitoxin (not available)
- ? Steroids
- Treat for 60 days total

# Recommended Initial\* Anthrax Treatment

	Therapy	Duration
Cutaneous	Ciprofloxacin 500mg BID PO OR Doxycycline 100 mg BID PO	14 days
Inhalation	Ciprofloxacin 400 mg IV BID OR Doxycycline 100 mg BID IV	14 days, may switch to PO when clinically appropriate

Ciprofloxacin or doxycycline also recommended as initial therapy for children in appropriate doses

\*Until antibiotic susceptibility test results available

# Recommended Postexposure Antibiotic Prophylaxis for Prevention of Inhalation Anthrax

	Initial Therapy	Duration
Adults (including pregnant women and immunocompromised)	Ciprofloxacin 500 mg PO BID OR Doxycycline 100 mg PO BID	60 days
Children	Ciprofloxacin 10-15 mg/kg PO Q 12 hrs OR Doxycycline: >8 yrs and >45 kg: 100 mg PO BID >8 yrs and ≤45 kg: 2.2 mg/kg PO BID ≤8 yrs: 2.2 mg/kg PO BID	60 days

# Control / Prevention

**Human disease is controlled by:**

- Reducing infection in livestock**
- Supervised slaughter and meat inspection**
- Reducing exposure through import restriction, biosafety precautions, education**
- Vaccination of high-risk human populations**
- Treatment and post-exposure prophylaxis**

# Anthrax Vaccine

## US Vaccine: BioThrax or Anthrax Vaccine Adsorbed

- Cell-free filtrate of a nonencapsulated, toxigenic strain of *B. anthracis*
- Produces humoral response against protective antigen
- Preexposure vaccination schedule: 6 doses SQ at 0,2,4 weeks, 6,12,18 months with yearly booster
- Postexposure vaccination schedule: 3 doses SQ at 0,2,4 weeks + 60 days of antibiotics
- Precautionary use in immunosuppressed individuals
- Contraindicated for pregnant women

# Human Anthrax Vaccine Trial

Brachman PS *et al.* Field Evaluation of a Human Anthrax Vaccine. 1962.  
*Am J Pub Health* 52: 632-645.

- Randomized adjuvant control trial using alum vaccine
- 4 mills processing goat hair
- 379 vaccinated and 870 controls
  - 3 cases (cutaneous) in vaccinated group: 2 had not completed series
  - 23 cases in unvaccinated group, 5 inhalation
  - 93% efficacy (95%CI = 65% to 95%)

# Animal Studies of Post-exposure Prophylaxis

- Henderson, et al (1956): Alum precipitate PA filtrate vaccine

Methods: 5 days of penicillin compared to penicillin with postexposure vaccination

Results: 9 of the 10 receiving only penicillin died, while all of the macaques receiving penicillin and vaccine survived

- Friedlander et al (1993): Aluminum hydroxide PA filtrate vaccine

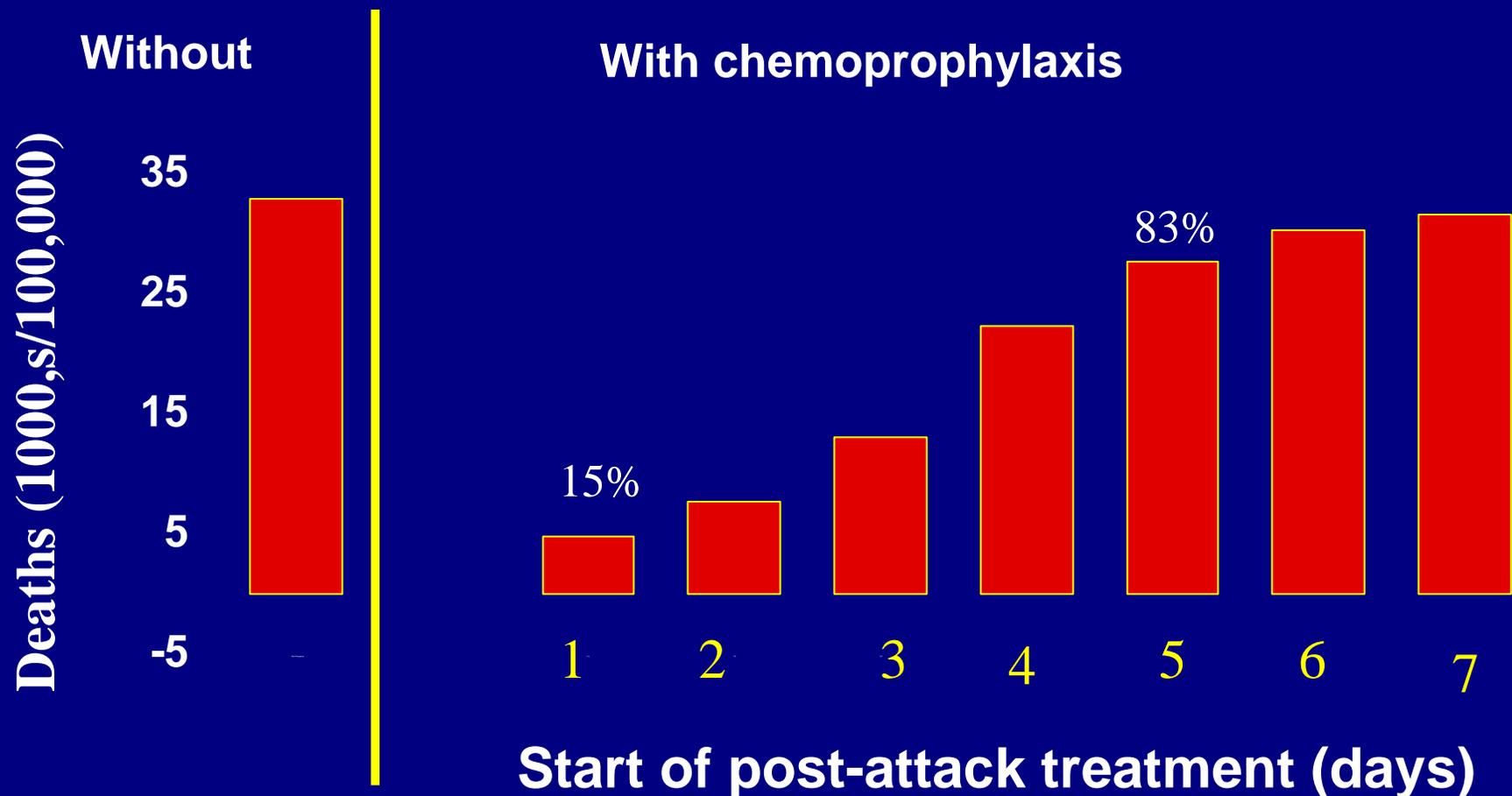
Methods: 30 days of various antibiotics compared to 30 days of doxycycline with postexposure vaccination

Results: 9 of the 10 animals in the doxycycline-alone arm survived, while all receiving doxycycline and vaccine survived

# Anthrax Vaccine Safety

- Mild local reactions (tenderness, swelling, nodule formation) occur in 30% - 60% of recipients
- Large local reactions occur in  $\leq 1\%$  of vaccinees
- Systemic reactions: 5%-35% experience muscle ache, joint ache, headache, malaise, fever
- Serious side effect profile similar to other vaccines given to adults (influenza and hepatitis)

# Deaths with and without post-exposure prophylaxis following an anthrax release

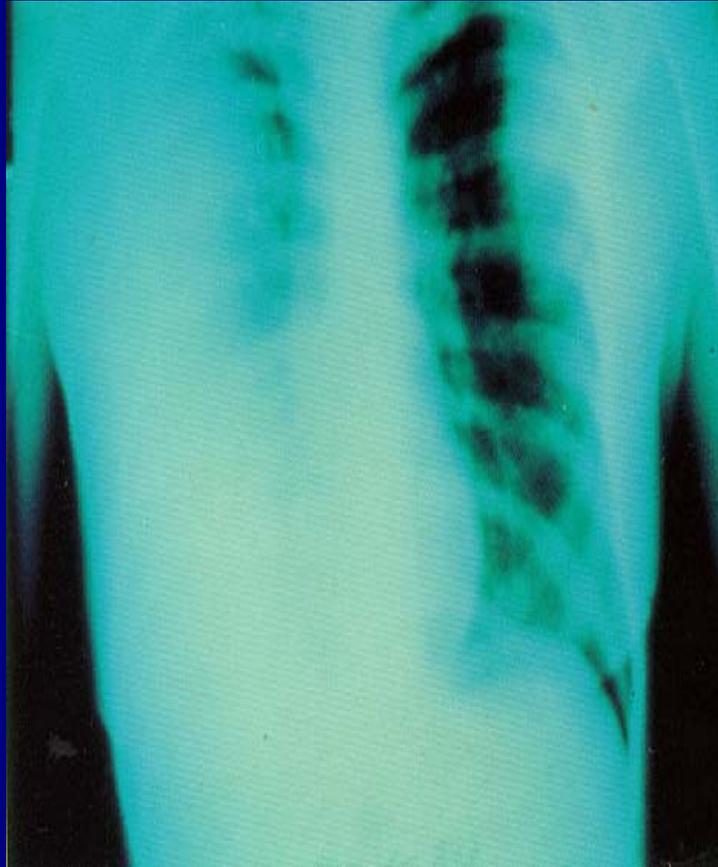


Source: Kaufmann AF, Meltzer MI, Schmid GP. *Emerging Infect Dis* 1997; 3:83-94.

# Case Study 1

- It is 5pm on a Friday afternoon in December and you are getting ready to go a Christmas party with your family. Your last appointment of the day is a 53 year old male office worker with the following complaints:
  - Headache, malaise, muscle ache, feels feverish and having some difficulty breathing
- Your exam findings: absence of breath sounds on the right side of the thorax, crackles on the left side, body temperature 37.5° C

# Chest X-Ray Results



What is on your list of differential diagnoses?

- You hospitalize the patient; his condition worsens rapidly with dyspnea, cyanosis, and hemoptysis
- What samples should you consider collecting?

# Specimen Selection is Important

## Anthrax

- Blood or cerebrospinal fluid – gram stain
- Pleural fluid – request immunohistochemical staining

## Tularemia

- Serum for antibody titer
- Pharyngeal wash or sputum specimen for culture, direct fluorescent antibody, organism gram stains poorly

## Pneumonic Plague

- Sputum/throat or bronchial washings- request Wayson stain to see bipolar organism, or direct fluorescent antibody of smear

Case Study 2: A US tourist comes to see you with this lesion on her arm.  
What questions would you ask this patient?



Seven days after her first visit, she comes to see you again.  
The lesion now looks like this – what is on your list of  
differential diagnoses?



# DO NOT PANIC !

- Individuals must be exposed to *B. Anthracis* spores
- To cause disease, *B. anthracis* spores must enter the skin, be swallowed, or inhaled
- Disease can be prevented after exposure to anthrax spores by early treatment with appropriate antibiotics
- Anthrax is NOT spread from person to person

# Anthrax Information

- [www.aad.org/BioInfo/Biomessage2](http://www.aad.org/BioInfo/Biomessage2)
- [www.who.int/emc-documents/zoonoses/docs](http://www.who.int/emc-documents/zoonoses/docs)
- [www.bt.cdc.gov](http://www.bt.cdc.gov)

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