

Responding to the Threat of Bioterrorism: A Status Report on Vaccine Research in the United States

Dixie E. Snider, M.D., M.P.H.
Associate Director for Science
Centers for Disease Control and Prevention

Biological Terrorism: Why Be Concerned Now?

- Low tech, low expense
- Multiple means of dissemination
- Developed as biological weapons
- Economic, political, religious polarization
- Contagiousness/lack of immunity
- Diseases unfamiliar/covert action easy
- Potential for panic/economic impact



Biological Agents of Highest Concern

- *Variola major* (Smallpox)
- *Bacillus anthracis* (Anthrax)
- *Yersinia pestis* (Plague)
- *Francisella tularensis* (Tularemia)
- Botulinum toxin (Botulism)
- Filoviruses and Arenaviruses (Viral hemorrhagic fevers)

Other Potential Threats

- BACTERIAL
 - Brucellosis
 - Q fever
 - Glanders
 - Melioidosis
 - Food/water borne pathogens
- VIRAL
 - Viral encephalitidies
- TOXINS
 - Staph Enterotoxin B
 - Ricin
 - Tricothecene mycotoxins
- UNKNOWNNS
 - Genetically altered agents
 - New chemicals
 - Others

Why These Agents?

- Infectious via aerosol
- Susceptible civilian populations
- High morbidity and mortality
- Person-to-person transmission (smallpox, plague, VHF)
- Difficult to diagnose and/or treat
- Previous development for BW



Anthrax: Overview

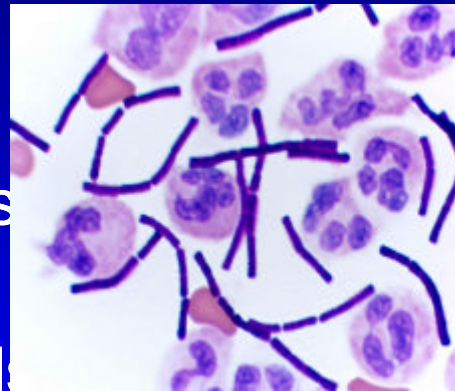
- Primarily disease of herbivores
- Humans contract disease by contact with infected animals or contaminated animal products
- Soil reservoir worldwide
- No person-to-person transmission of inhalational anthrax
- Cutaneous, gastrointestinal, and inhalational forms
- Inhalational form >85% mortality



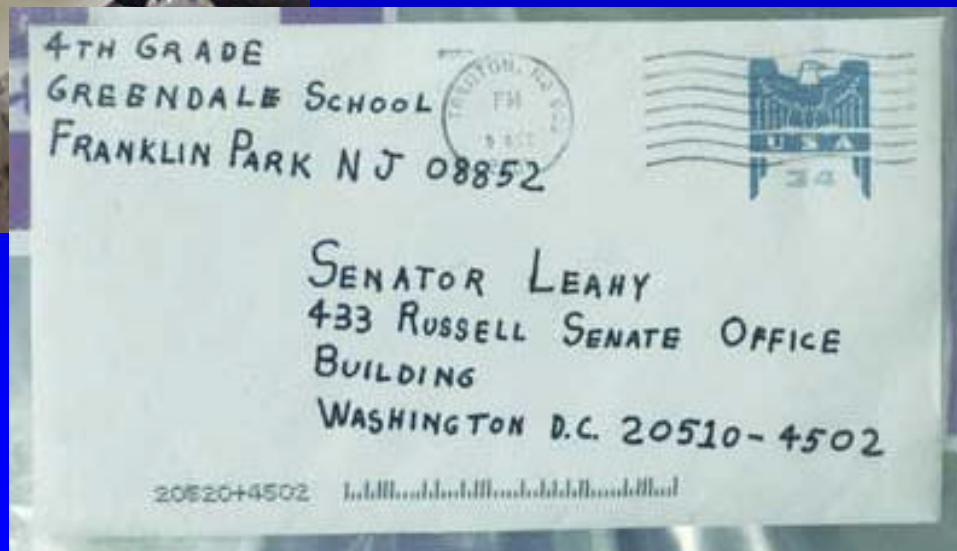
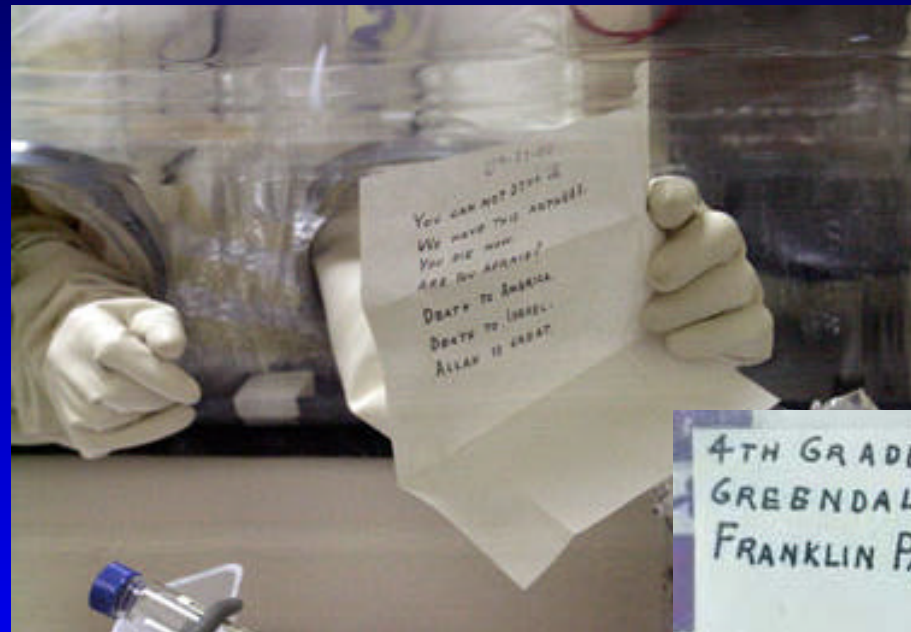
Recognition in Florida

Inhalational anthrax

- 63 yo male photo editor employed by AMI
- Onset 9/30
 - Fever
 - Altered mental status
 - Admission 10/2
 - CSF with gram + rods
 - Positive blood and CSF cultures
- CDC notification 10/3
- Autopsy consistent with inhalational anthrax on 10/6



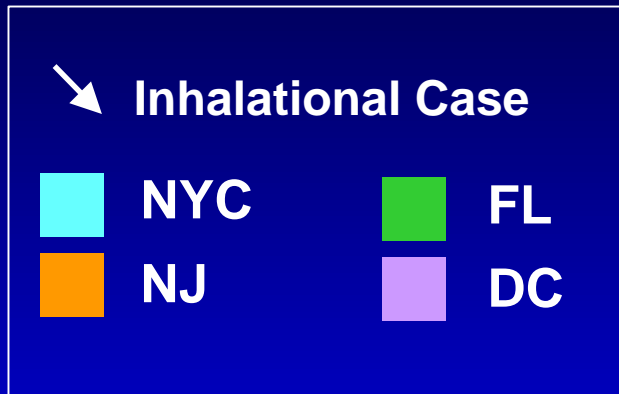
Senator Daschle & Leahy Envelopes: Postmarked 10/9/01



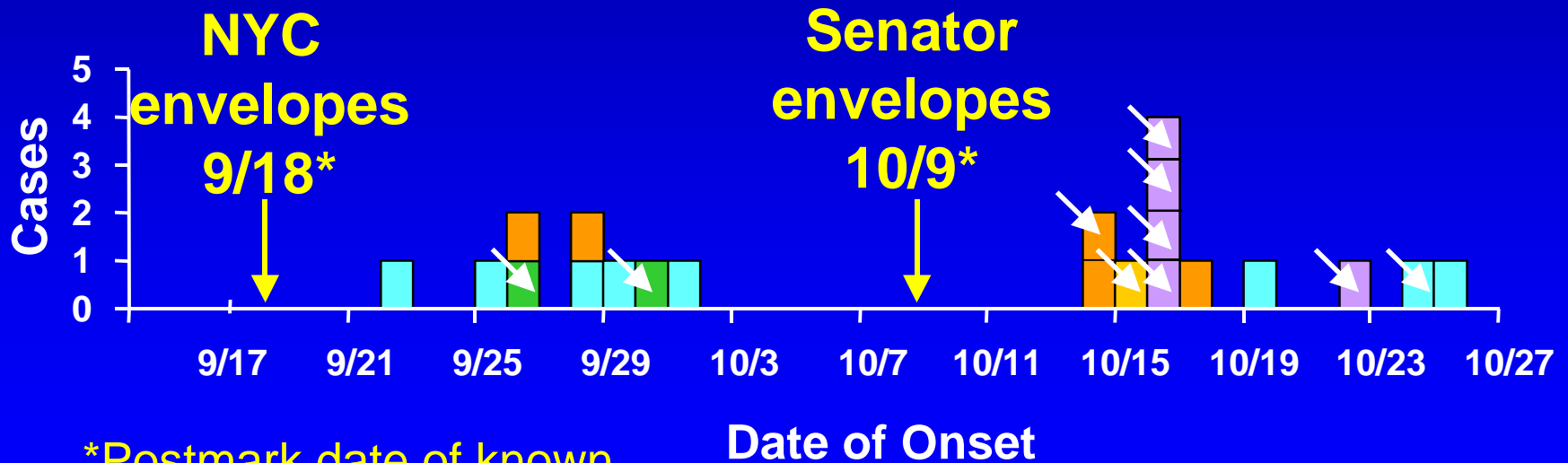
Anthrax Bioterrorism Investigations, 2001-2002



Bioterrorism-associated Anthrax: Inhalational and Cutaneous Cases



CT inhalational anthrax case, date of onset - 11/14



*Postmark date of known contaminated envelopes



Anthrax: Treatment

- Antibiotics (combination therapy)
 - ciprofloxacin or doxycycline,
and 1 or 2 of the following:
 - Penicillin (if PCN susceptible), rifampin, vancomycin, ampicillin, chloramphenicol, imipenem, clindamycin, clarithromycin
- Supportive care
- Standard precautions, no need for quarantine/isolation
- Duration of treatment dependent on form of anthrax and types of exposures
- Early treatment improves prognosis

Anthrax: Post-Exposure Prophylaxis

- Start oral antibiotics soon (<24 hours) after exposure
 - Ciprofloxacin
 - Doxycycline
 - Amoxicillin or Penicillin (if known PCN sensitive)
- Antibiotics for up to 100 days without vaccine
- Antibiotics until 3 doses of vaccine given (0, 2, 4 weeks) ~ 40 days

Smallpox: Overview

- 1980 - Global eradication
- Humans only known reservoir
- Person-to-person transmission (aerosol/contact)
- Up to 30% mortality in unvaccinated

Smallpox: Management

- Supportive care
- ?Role of antiviral agents
- Strict respiratory/contact isolation of patient
 - Patient infectious until all scabs have separated
- Immediate vaccination of ALL close contacts
 - All contacts within 17 days of the onset of case's symptoms
- Surveillance of contacts for 17 days

Plague: Overview

- Natural vector - rodent flea
- Mammalian hosts
 - Rats, squirrels, chipmunks, rabbits, and carnivores

About 10-15 cases/year U.S.
(all forms)

- Mainly SW states

Bubonic, pneumonic, and
septicemic forms



CDC

Plague: Medical Management

- Antibiotic therapy - Gentamicin, Streptomycin, Tetracyclines, Sulfonamides, Chloramphenicol (meningitis/pleuritis)
- Supportive therapy
- Isolation and droplet precautions for pneumonic plague until sputum cultures negative
- Contacts of pneumonic cases and those exposed at same time as index case given chemoprophylaxis – Doxycycline, Tetracycline or TMP/SMX
- Vaccine no longer manufactured in the U.S.

Tularemia: Overview

- Disease of Northern Hemisphere
- In U.S., most cases associated with rabbits/hares and ticks
- ~ 200 cases/year in U.S.
 - most in South central and Western states
 - majority of cases in summer, some in winter
- Low infectious dose
 - 1 to 10 organisms by aerosol or intradermal route
- No person-to-person transmission



Tularemia: Clinical Forms

- Ulceroglandular
 - Ulcer with regional adenopathy
- Glandular
 - Regional adenopathy without skin lesion
- Oculoglandular
 - Painful purulent conjunctivitis with adenopathy
- Typhoidal
 - Septicemia, no adenopathy
 - Possible initial presentation for BT
- Pneumonic (primary or secondary)
 - Possible initial presentation for BT

Tularemia: Treatment/Prophylaxis

- Treatment
 - Streptomycin or Gentamicin
 - Tetracyclines
- Prophylaxis
 - Fever watch for 7 days (preferable)
 - Doxycycline or Tetracycline for 14 days if febrile
- Vaccine investigational, not available

Viral Hemorrhagic Fevers (VHF): Overview

- Caused by several different viruses families
 - **Filoviruses** (Ebola, Marburg)
 - **Arenaviruses** (Lassa, Junin, Machupo, Sabia, Guanarito)
 - Bunyaviruses
 - Flaviviruses
- Natural vectors - virus dependent
 - rodents, mosquitoes, ticks



VHF: Clinical Presentation

- Usual patient history
 - Foreign travel to endemic or epidemic area in rural environment
 - Nosocomial exposure
 - Contact with arthropod or rodent reservoir
 - Domestic animal blood exposure
- Incubation
 - Typical 5 to 10 days (Range 2 to 16 days)
- Symptoms
 - Bleeding, CNS involvement
- Mortality agent dependent (10-90%)

Botulism: Overview

- Caused by toxin from *Clostridium botulinum*
 - Toxin types A, B, E, associated with most human disease
 - Most potent lethal substance known (LD = 1ng/kg)
- *C. botulinum* spores found in soil worldwide
- ~ 100 reported cases/year in the U.S.
 - Infant most common (72%)
 - Food-borne not common
- No person-to-person transmission

Botulism: Forms

- Foodborne
 - Toxin produced anaerobically in improperly processed or canned, low-acid foods contaminated by spores
- Wound
 - Toxin produced by organisms contaminating wound
- Infant
 - Toxin produced by organisms in intestinal tract
- Inhalation botulism
 - No natural occurrence, developed as BW weapon

Botulism: Clinical Presentation

- Incubation: 18 to 36 hours (dose dependent)
- Afebrile, alert, oriented; normal sensory exam
 - Early nausea, vomiting, diarrhea
- Cranial Nerve symptoms
 - Ptosis, blurry/double vision, difficulty swallowing/talking, decreased salivation
- Motor symptoms (progressive)
 - Bilateral descending flaccid paralysis → respiratory paralysis
- Death 60% untreated; <5% treated

Botulism: Treatment/Prophylaxis

- Ventilatory assistance and supportive care
- Botulinum antitoxin
 - Licensed trivalent equine product against types A,B, and E available from CDC
 - Most effective if given early
- Antibiotics for wound botulism
 - PCN
- Recovery and supportive care may be prolonged
- Toxoid vaccine investigational, not available
- Other botulinum antitoxins available as Investigational New Drugs (IND)

Anthrax Vaccine

- Current U.S. vaccine (FDA Licensed)
 - Culture supernatant containing Protective Antigen (PA) from attenuated non-encapsulated strain
 - Protective against cutaneous (human data) and possibly inhalational anthrax (animal data)
 - Licensed 6 dose regimen over 18 months; annual boosters
 - 3 doses (0, 2, and 4 weeks) appear effective for post-exposure treatment in combination with abx
 - Limited availability

Anthrax Vaccine Adverse Effects

- 30% or less with mild discomfort at inoculation site for up to 72 hours
 - tenderness, redness, swelling, or itching
- < 2% with more severe local reactions
 - potentially limited use of the arm for 1- 2 days
- Reactions more common in women
- Systemic reactions rare

New Approaches: Anthrax Vaccine

- Recombinant vaccines
- Mutant-strain vaccines
- Purified PA preparations + adjuvant

AVRP Human Reactogenicity and Immunogenicity Trial to Address Change in Route of Administration and Dose Reduction

Objectives:

To determine impact of AVA route of administration (SQ vs IM) on reactogenicity and immunogenicity among men and women, and

To evaluate the impact of AVA dose reduction from current total of 6 doses with annual booster, to 3 doses with booster every 3 years

Anthrax Vaccine Studies

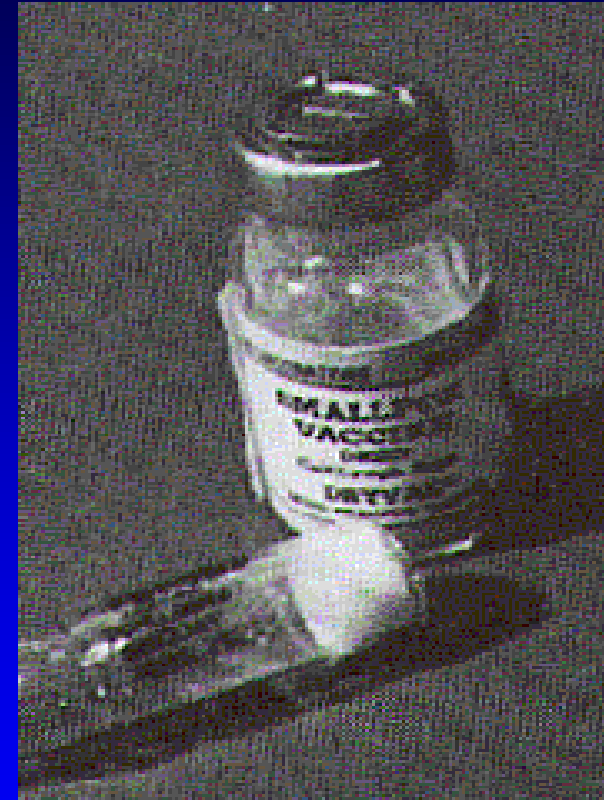
- Effect of different doses on immunogenicity and challenge in nonhuman primates (CDC, Battelle)
- Serological assays and studies of immune correlates of protection (CDC, FDA, NIH, USAMRIID, Battelle, Emory)
- National survey of KSA's regarding the anthrax vaccine among military personnel (CDC, DOD, RTI)
- Survey of health care providers regarding the vaccine and reporting of possible adverse events (CDC, FDA, DOD)

Anthrax Vaccine Studies

- Comparative evaluation of the effect of anthrax vaccine on health-related quality of life (CDC, DOD)
- Retrospective study of long –term adverse effects among vaccinated mill workers (CDC)
- Study of hormonal correlates of adverse events among female clinical trial participants (CDC, DOD)
- Studies of vaccine delivery and follow-up of adverse events (CDC, DOD, NVHCN)

Smallpox: Current Vaccine

- Live Vaccinia virus (not smallpox virus)
 - ~15 million doses in US stores
- ID inoculation with bifurcated needle (scarification)
 - Pustular lesion/induration surrounding central scab/ulcer 6-8 days post-vaccination
 - Low grade fever, axillary lymphadenopathy
 - Scar (permanent) demonstrates successful vaccination
 - Immunity not life-long



WHO

Smallpox Vaccination: Complications

- Approximately 25AR's/100,000 vaccinations
- Most common
 - Inadvertent inoculation (skin, eye, etc.)
- Less Common
 - Generalized vaccinia
 - Post-vaccination encephalitis (2.8/million)
 - Fetal vaccinia
 - Eczema vaccinatum (4.5/million)
 - Vaccinia necrosum (0.7/million)
- Primary vaccination - 1 death/million
- Revaccination - 0.2 deaths/million

Smallpox: Vaccinia Immune Globulin (VIG)

- Treatment of adverse reactions (AR)
- Post-exposure prophylaxis
 - Pregnant patients (VIG + Vaccinia vaccine)
 - Eczema (VIG + Vaccinia vaccine)
 - Immunocompromised patients, No consensus (VIG alone vs. VIG + Vaccinia vaccine)
- Current supplies very limited – reserved for treatment of severe AR's, not prophylaxis

Other Vaccines

- Plague Vaccine
 - Used effectively in WWII and Vietnam
 - May not protect against aerosol infection
 - Very reactogenic
- Tularemia Vaccine
 - Agent developed for BW
 - Questionable efficacy

Other Vaccines

- Viral Hemorrhagic Fevers
 - Vaccines at early stages of development
- Botulism Toxin
 - Pentavalent toxoid available under IND
 - Local reactions increases as number of doses increase
 - Types F and G toxoids absent
 - High cost

Bioterrorism Vaccine Issues

- Should we invest in developing these vaccines?
- Who has responsibility for R&D and production– ie, roles of government, academia, private industry developing and evaluating vaccines for BT threats?
- Impediments to R&D and production – select agent rule, limited facilities, limited resources
- How can we assure R&D will not lead to unintended adverse effects?
- How do we set priorities among the agents?

Bioterrorism Vaccine Issues

- How do we determine efficacy? Role of animal models and in vitro studies
- How will we obtain safety data prior to licensure and how much will be enough?
- How will we organize and implement safety and efficacy studies post-licensure?
- How will we develop protocols and consent forms? Who should be involved in the review, how do we engage them, and how do the IRBs assimilate and incorporate them?
- For licensed products, will “off-label” use be permitted?. Who has responsibility for developing and evaluating vaccines for BT threats?
- Would importation of a vaccine unlicensed in the U.S. ever be considered?



Bioterrorism Vaccine Issues

- Who will pay for the purchase and distribution the vaccines?
- Who will distribute and administer the vaccines?
- How will we ensure appropriate and fair distribution?
- How will guidelines for use of vaccines be developed?
- Should vaccine be stockpiled or administered or is a combination approach the most appropriate
- Who should be targeted for vaccine and when should they be vaccinated (e.g., pre-exposure vs. post-exposure)?

Bioterrorism Vaccine Issues

- Should vaccination be mandatory or permissive and how does risk of attack and necessity of quarantine affect that decision?
- Can we maintain the principle of autonomy in such an environment?
- How can we obtain true informed consent in a situation in which risk data is considered protected by national security concerns?
- Who assumes liability for vaccine-related injury?