Bioterrorism: Medical and Public Health Perspectives

Marcelle Layton, MD
NYC Department of Health and Mental Hygiene

Why There Was a Belief that Bioterrorism in the U.S. Would Never Happen

- Biologic weapons seldom used
- Their use is morally repugnant
- Technologically difficult
- Concept was “unthinkable” and thus dismissed

Biowarfare\Bioterrorism: Historical Perspectives

- 1347: Tartar Siege of Kaffa: Catapulting of plague victims over city walls
- 1700s: British and Native Americans: Blankets contaminated w\ smallpox
- 1985: Dulles, Oregon – Salmonella contamination of salad bars by Rajneesh cult

Biological Warfare

- 1943-1969 - US had active offensive program
- In 1972, U.S. and many other countries signed the Biological Weapons Convention
- Former Soviet Union program began massive production program effort in 1970s

International Bioweapons Programs

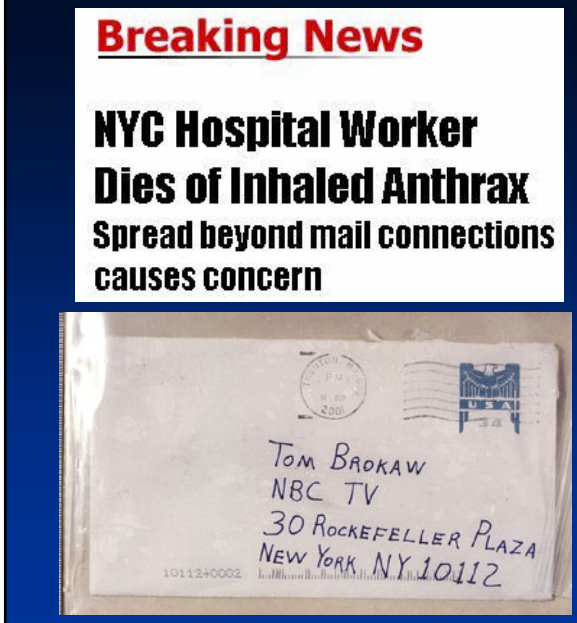
Known: Iraq, Former Soviet Union

Probable: China, Iran, N Korea, Libya, Syria

?'ble: Israel, Egypt, Cuba

ATCC supplied seed stock for Iraq's program

September 11, 2001



Why Use Biological Agents?

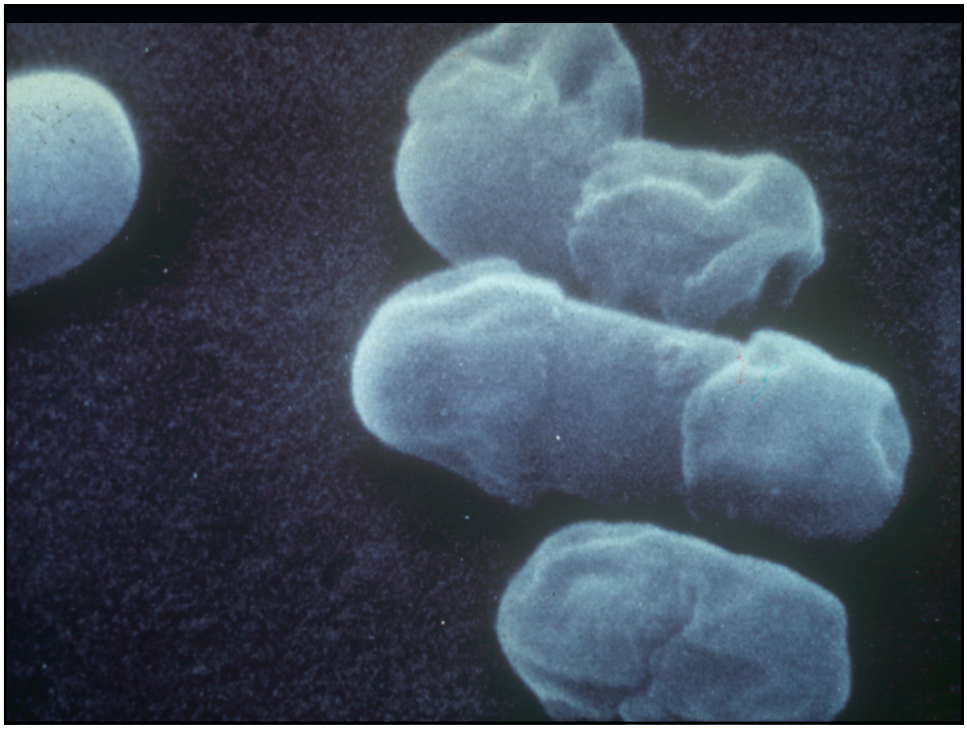
- Potential for dissemination over wide area
- Mass casualties at low cost
- Perpetrators can protect themselves and delayed onset can allow time for escape
- Panic in the streets

Ideal Characteristics for Potential Biologic Agent

- Silent, odorless, tasteless
- Inexpensive and easy to produce
- Can be aerosolized (1-10 um)
- Survives sunlight, drying, heat
- Causes lethal or disabling disease
- Person to person transmission
- No effective Rx or prophylaxis

Biowarfare/Bioterrorism: Potential Agents

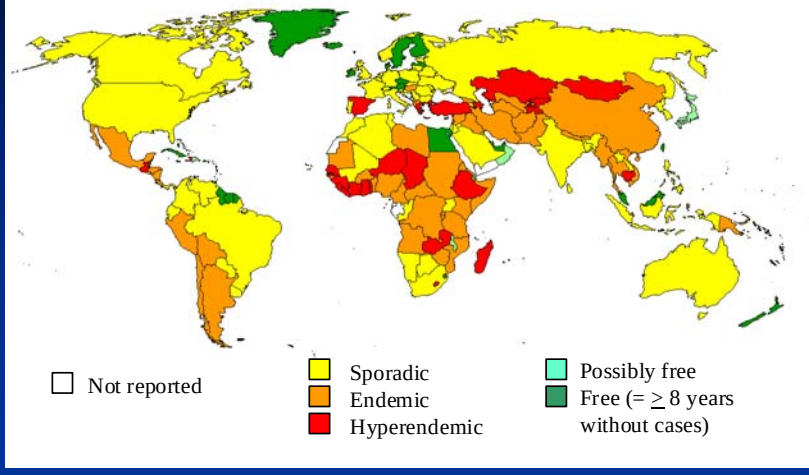
- Bacterial: Anthrax, Brucellosis, Plague, Q fever, Tularemia
- Viral: Smallpox, Viral Hemorrhagic Fever
- Toxin: Botulism, Ricin, Staph. enterotoxin B



Anthrax

- Caused by *Bacillus anthracis*, a non-motile Gram-positive rod
- Natural disease of herbivores
- Produces three exotoxins:
  - Edema factor
  - Lethal factor
  - Protective antigen
- Not contagious

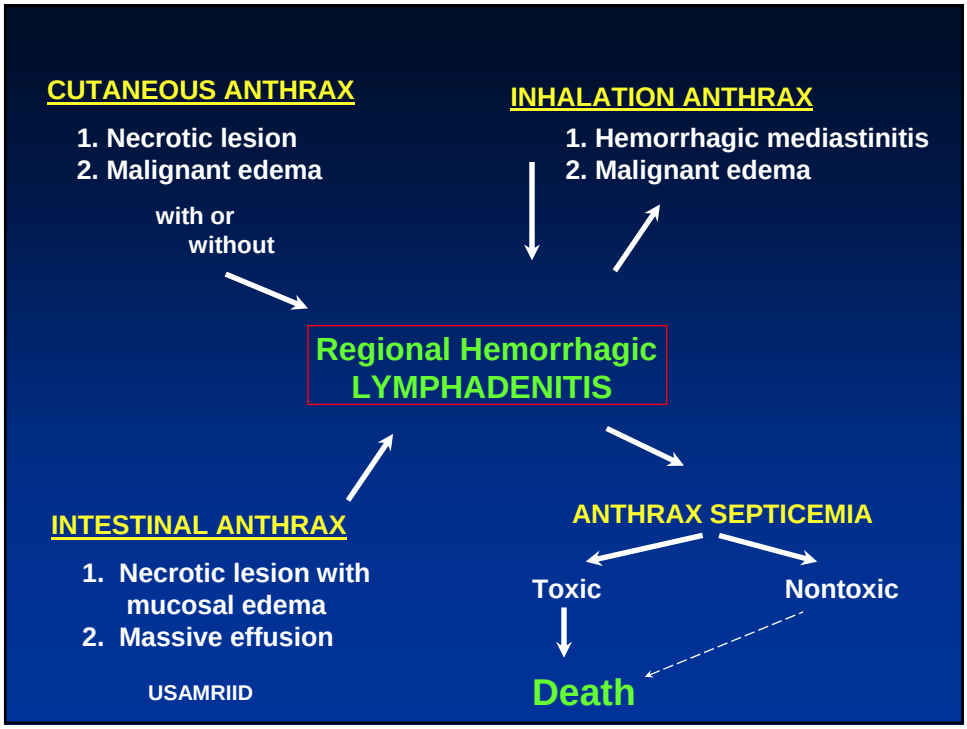
Anthrax status, 1998



Merck; Hugh Jones

Anthrax as a Biologic Weapon: Potential Significance

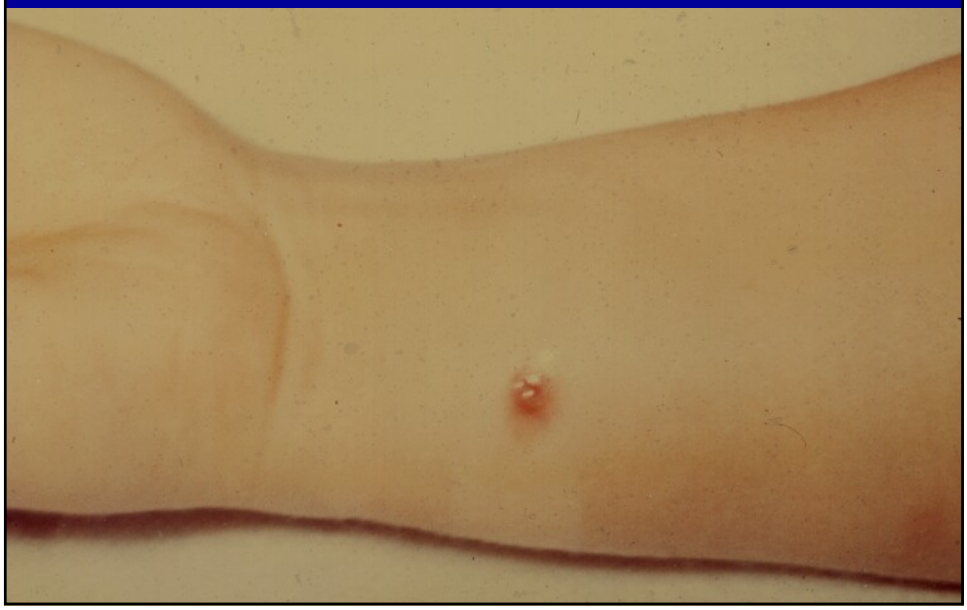
- Spores remain viable for years
- Aerosolization can cause inhalational anthrax - a severe, often fatal necrotizing mediastinitis
- Has been weaponized by U.S. (1950s), USSR (1950s to 1992) and Iraq (1995)



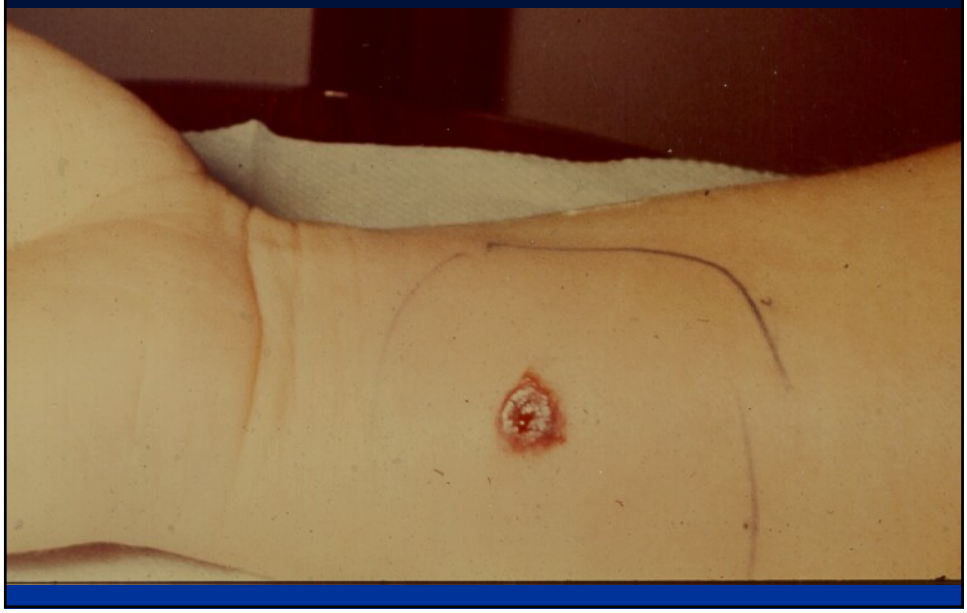
Cutaneous Anthrax

- Route of infection: Direct inoculation of spores
- Incubation period: 1-7 days (may be up to 14 d)
- Clinical findings
  - Pruritic macule ➡ vesicle ➡ round ulcer . ➡ black eschar over 1-2 weeks
  - Surrounding edema/erythema but painless
  - +/- painful regional lymphadenopathy
- Untreated, ~ 5%-20% fatality rate

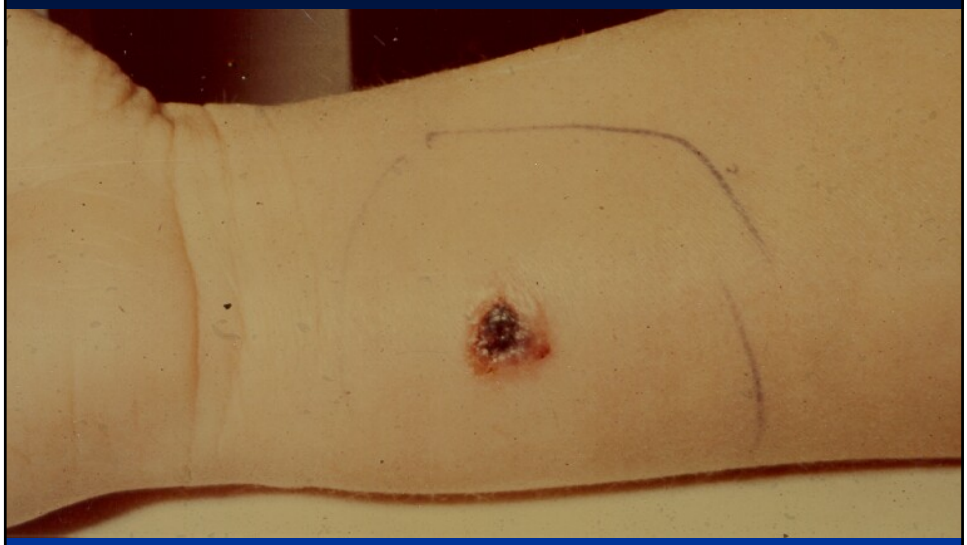
Cutaneous Anthrax – Day 4



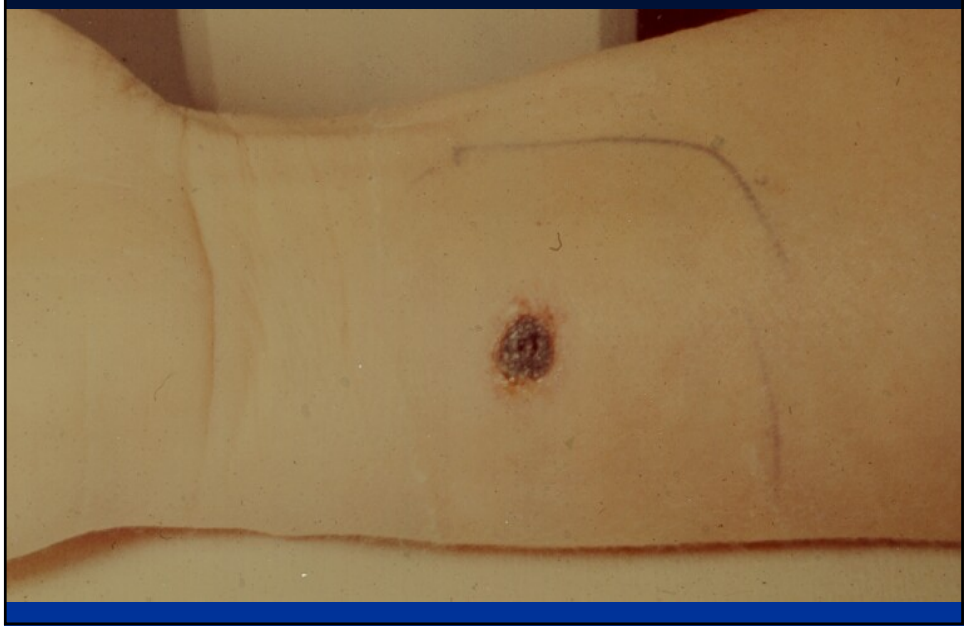
Cutaneous Anthrax – Day 5



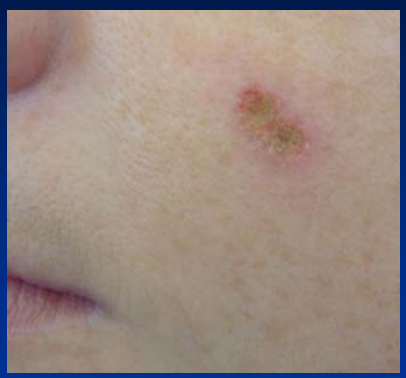
Cutaneous Anthrax – Day 7

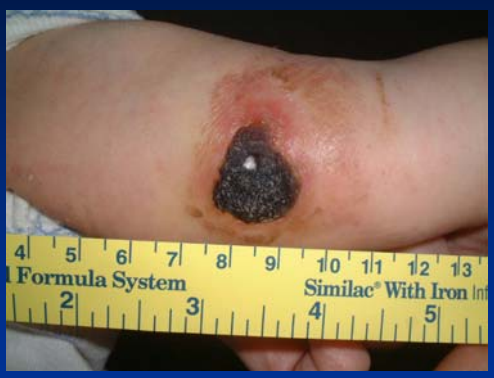


Cutaneous Anthrax – Day 10



Varying Presentations of NYC Cutaneous Lesions





Cutaneous Anthrax: Diagnosis

- Vesicular fluid or border of skin lesion:
  - Gram stain, culture and sensitivity
  - PCR
- Skin biopsy
  - Culture and PCR (fresh frozen)
  - Immunohistochemistry (formalin-fixed)
- Serology:
  - Acute- and convalescent-phase serum IgG (ELISA IgG antibody against protective antigen)

Inhalational Anthrax

- Only 18 cases in US during 1900s (last in 1978)
- Route of infection: Inhalation of spores (1-5 microns in size) into terminal bronchioles and alveoli
- Incubation period ~ 1-6 d (range 1- ?100 d)

Pathogenesis

- Once deposited, inert spores reside within alveoli (days – weeks)
- Spores taken up by alveolar macrophages → regional lymph nodes
- Spores germinate, producing vegetative cells that proliferate within macrophages, produce toxins and enter the bloodstream

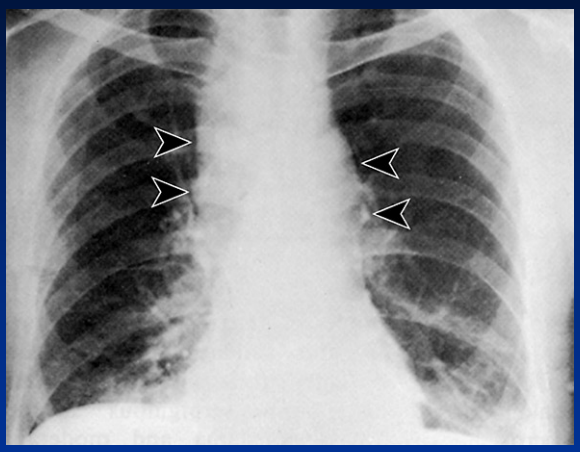
Inhalational Anthrax: Clinical Features

- Initial symptoms resemble “flu”
- Late symptoms include high fevers, vomiting, respiratory distress, and necrotizing hemorrhagic mediastinitis
- Fatal within 24-36 hours if treatment delayed

Diagnosis of Inhalational Anthrax

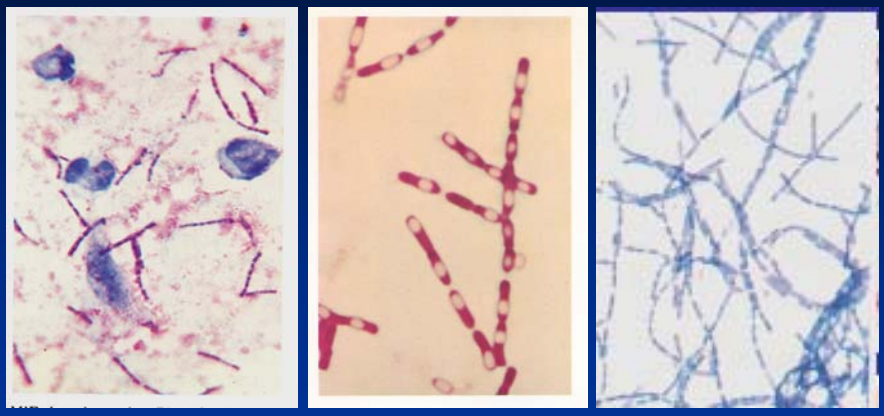
- Non-specific physical findings
- CXR: mediastinal adenopathy, pleural effusions
- Gm stain/culture (or PCR) of blood, pleural fluid, and CSF
  - Large Gm (+) rods
  - Rough, grayish colonies - non-hemolytic, non-motile
- Suspect cultures should be sent to NYCDOH/CDC

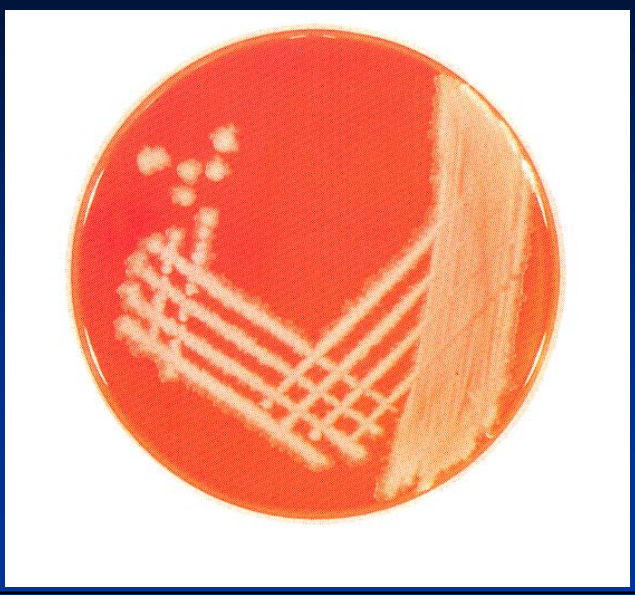
Inhalation Anthrax



Merck

Microbiologic Stains





Inhalational Anthrax Treatment

- Antibiotics are effective against vegetative *B. anthracis* but not against the spore form
- 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 (*including combination therapy)*

Anthrax Vaccine (Licensed in 1970)

- Culture supernatant (protective antigen) of attenuated, non-encapsulated strain
  - Protective against cutaneous (human data) and *possibly* inhalational anthrax (animal data)
  - Injections at 0, 2, 4 wks & 6, 12, 18 mos; followed by yearly boosters
  - 83% serologic response after 3 doses, 100% after 5
  - Current vaccine supplies are limited

Prevention of Inhalational Anthrax

- Primary prevention

  Vaccination of persons most at risk for exposure to anthrax spores

- Post exposure prophylaxis

  Vaccination of persons who have been exposed to aerosolized anthrax spores to prevent delayed spore germination and inhalational disease

Recent/Current Use of Anthrax Vaccine

Pre-exposure

- US military starting in 1997
- Personnel in CDC's Laboratory Response Network
- Decontamination workers
- Other occupations with high risk of exposure to potentially infected animals

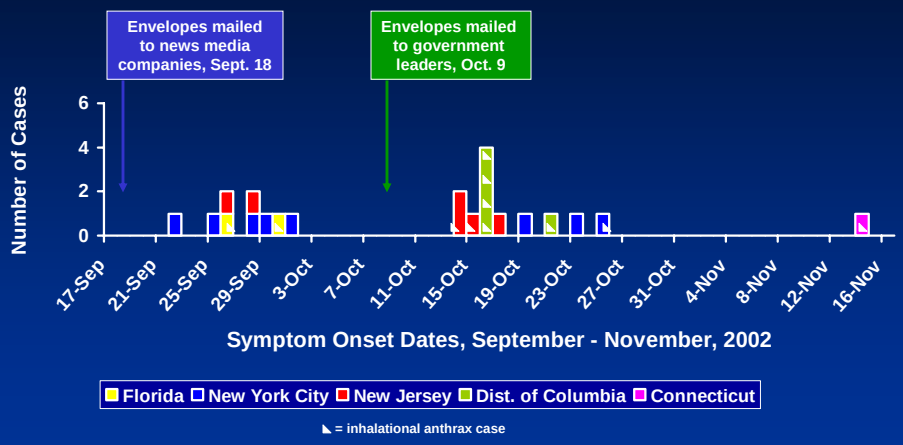
Post-exposure

- Victims of 2001 anthrax attack

Anthrax: Post-Exposure Prophylaxis

- Disease can be prevented as long as therapeutic antibiotic levels maintained until all spores cleared or controlled by immune defenses
- Viable spores demonstrated in mediastinal lymph nodes of monkeys 100d post-exposure
- Start oral antibiotics ASAP after exposure
  - Antibiotics for 100 days without vaccine
  - Antibiotics for 30 days with 3 doses of vaccine (0, 2 and 4 weeks)

Bioterrorism-Related anthrax, United States, 2001



Target of Terrorism is Public's Mental Health

Powders, Powders Everywhere…

The Impact of the Worried Well on the Public Health and Medical Systems

Sverdlovsk

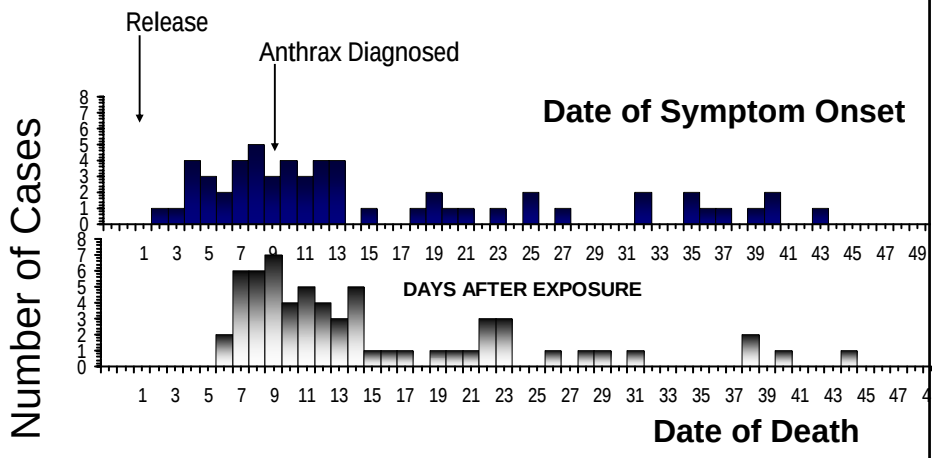
- City of 1.2 million people
- April 2, 1979: Anthrax outbreak reported
  - 79 "gastrointestinal" with 64 deaths
  - 17 cutaneous with no deaths
- 1992: Yeltsin acknowledges this was an inhalational outbreak due to explosion at a military facility

Sverdlosk Anthrax Outbreak*

- ? Release of < 1 gm of anthrax spores
- At least 77 cases identified; 66 (86%) fatal
  - All lived/worked within 4 km of bioweapons facility
  - No cases < 24 years
- Onset from 4 to 45 days after exposure
- Death occurred within 1-4 days of onset

** Meselsohn m. et al. Science Nov 18, 1994*

Inhalational Anthrax--Sverdlovsk, 1979



Sverdlovsk

- Ovals indicate estimated isodose lines of relative size 10, 5, 1.
- Letters indicate towns where animal anthrax was noted.

Merck; Hugh Jones

Smallpox: An Unexpected Re-Emerging Public Health Issue

Why an eradicated disease is considered a terrorist threat?

- 1980: WHO declares smallpox eradication
- Only WHO sanctioned repositories are at CDC and in Koltsovo, Siberia
  - BUT, weaponized by Soviets in 1970s-1990s
  - AND, security of Soviet material uncertain
  - ? recent media reports re: intelligence information suggesting that 4 countries have hidden stocks of virus

Smallpox as a Bioterrorist Weapon: Potential Significance

- Infectious via aerosol
- Rapid person-to-person transmission
- Worldwide immunity has waned
- Severe morbidity and mortality
- Clinical inexperience
- Potential to overwhelm medical care and public health systems (*large-scale vaccine campaigns*)

Transmission Factors

- Transmissible by droplet nuclei or aerosol, or via direct contact with oral/pustular fluid
- Less contagious than measles/varicella as patients often confined to bed by prodromal symptoms
- Historically, outbreaks occurred in households, but not in schools or workplace

Epidemiology of Smallpox

- Persons at most risk are household contacts
  - Attack rate among susceptible household contacts is ~58% (range 38%-88%)
- 2º spread to about 1-10 persons per case

Epidemiologic Factors Tempering Smallpox Concerns

- Incubation period 12-14 d (range 7-17 d)
- Vaccination of contacts within 4 days of exposure is effective in preventing illness
- Contagiousness begins with onset of rash
- Isolation measures effective in controlling outbreaks even with limited vaccine use

Smallpox Pathogenesis

- Implantation on oral or respiratory mucosa
- Migration to regional lymph nodes
- Initial asymptomatic viremia – day 3 or 4
- Multiplication in reticuloendothelial tissues
- Secondary symptomatic viremia – ~ day 8

Smallpox: Clinical Features

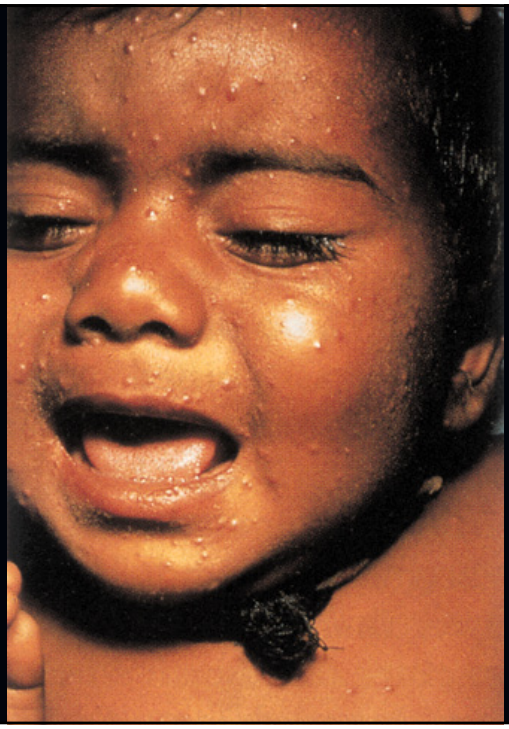
- Incubation period is 12-14 days (7-17d)
- Abrupt onset of high fever, malaise, rigors, vomiting, backache, and headache
- Followed in 2-3 d by maculopapular rash
- Generally not infective until rash appears

Smallpox: Exanthem

- Maculopapular rash
- Starts on face (*including oral mucosa*), forearms, or pharynx (centrifugal distribution)
- Spreads to trunk and legs
- Lesions on palms and soles common
- Macules/papules → vesicles → pustules
- Synchronous development
- Deeply embedded in dermis

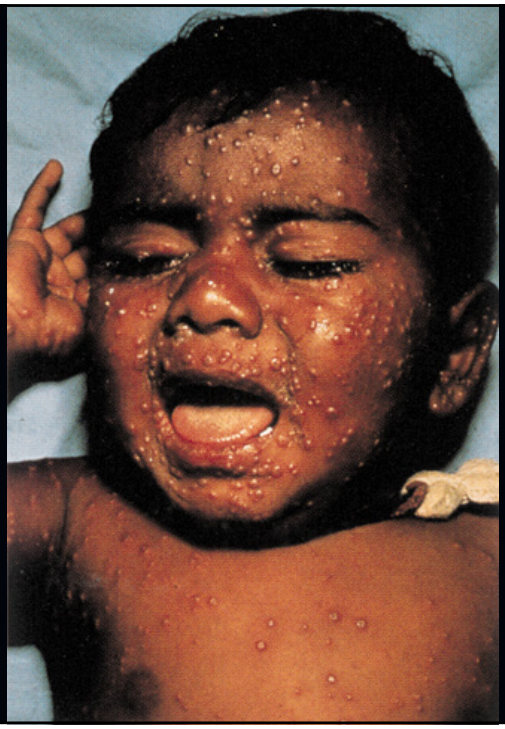
Variola Major

- Unvaccinated
- 3rd day of exanthem
- 12 days after exposure



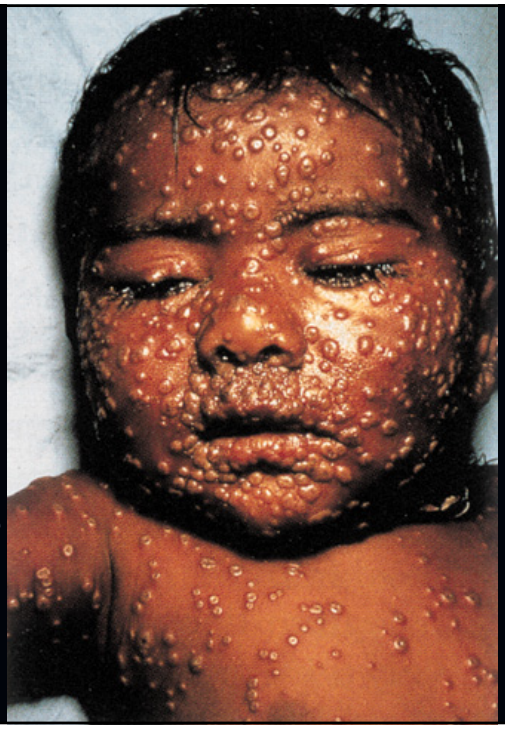
Variola Major

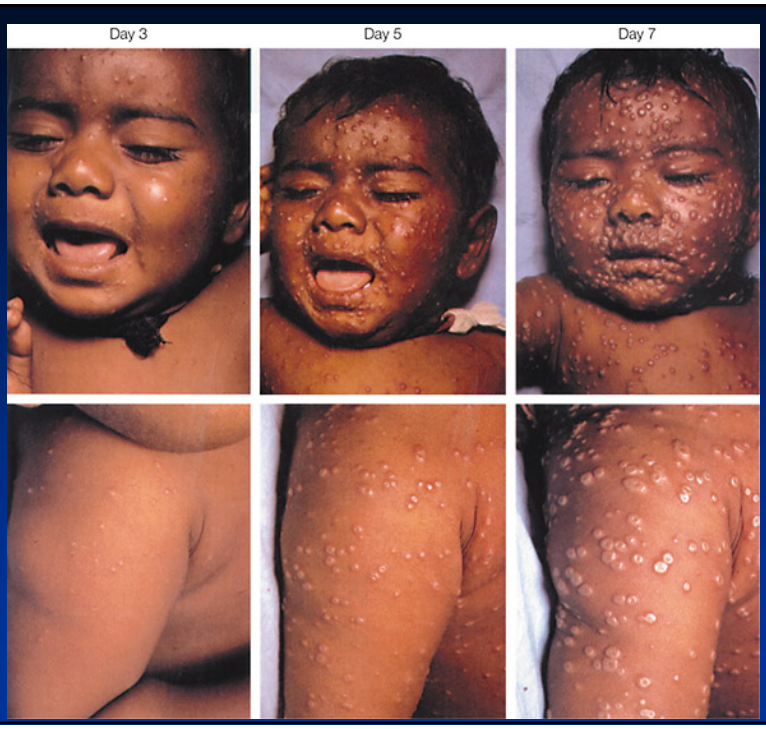
- 5th day of exanthem
- 14 days after exposure

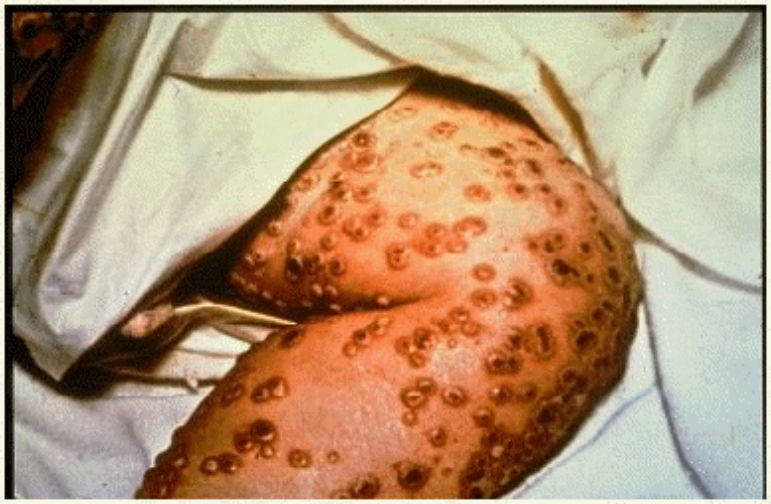


Variola Major

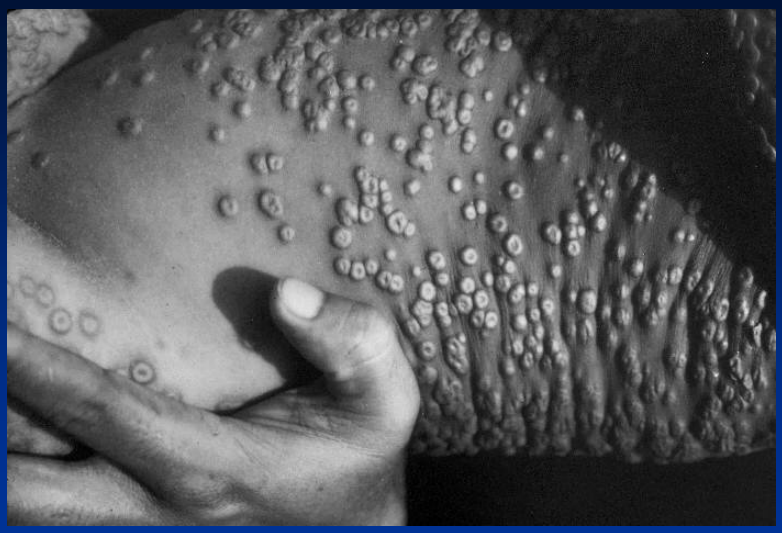
- 7th day of exanthem
- 16 days after exposure
- All lesions umbilicated and at the same stage of development

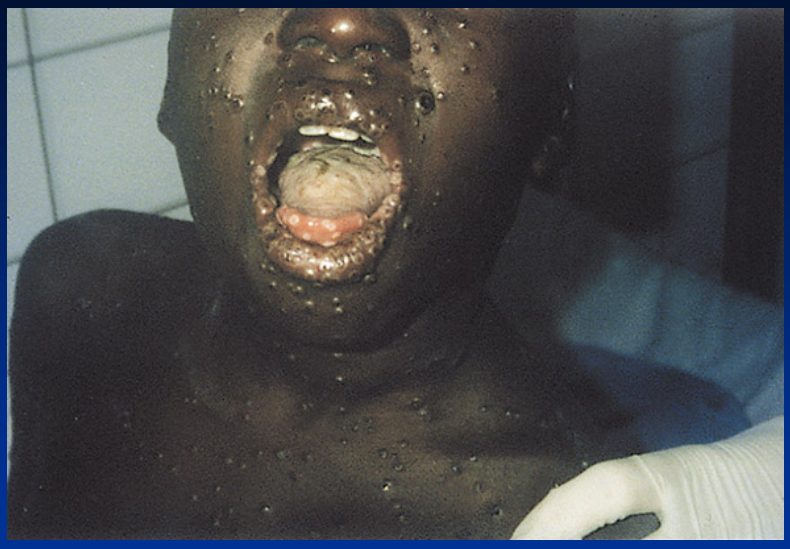






Patient's leg covered in smallpox





Diagnosis of Smallpox

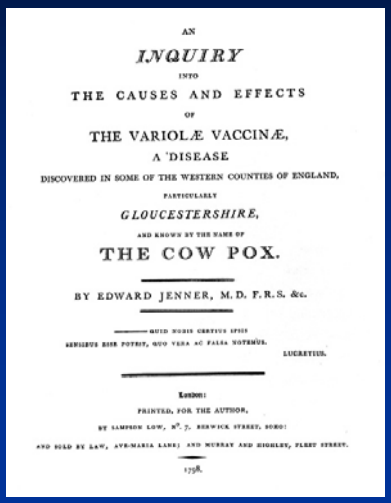
- Requires astute diagnostician to distinguish from varicella or erythema multiforme
- Swab of vesicular/pustular fluid or removal of scab for culture, EM, variola-specific PCR assay at CDC BSL4 laboratory

Smallpox vs Chickenpox

	Variola	Varicella
• Incubation	7-17 days	14-21 days
• Prodrome	2-4 days	Minimal
• Distribution	Centrifugal	Centripetal
• Evolution	Synch	Asynch
• Depth of lesion	Dermal	SubQ

Smallpox: Medical Management

- Even one suspect case is an international emergency requiring immediate reporting to public health authorities
- Strict quarantine with both respiratory and wound isolation (*negative airflow pressure and HEPA filtration)*
- No proven Rx (*cidofovir effective in vitro)*



AN

INQUIRY

INTO

THE CAUSES AND EFFECTS

OF

THE VARIOLÆ VACCINÆ,

A DISEASE

DISCOVERED IN SOME OF THE WESTERN COUNTIES OF ENGLAND,

PARTICULARLY

GLOUCESTERSHIRE,

AND KNOWN BY THE NAME OF

THE COW POX.

BY EDWARD JENNER, M.D. F.R.S. &c.

LUCRETIUS.

London:

PRINTED, FOR THE AUTHOR,

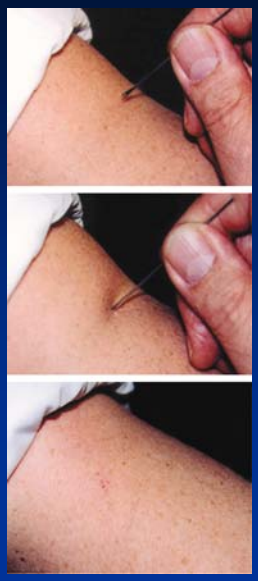
1798.

Smallpox Vaccine

- 1796: 1st vaccine developed by Edward Jenner
- 1972: US stops routine vaccination
- 1976: Routine vaccination of HCWs discontinued
- 1977: Somalia - last naturally occurring case
- 1980: WHO certifies the world free of smallpox
- 1982: Licensed vaccine producer stops production
- 1990: US military stops routine vaccination

Vaccinia (Dryvax) Vaccine

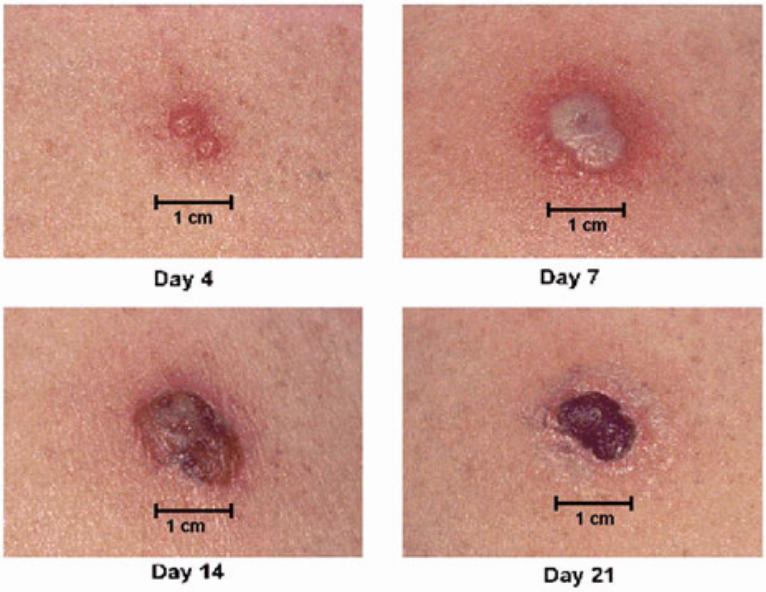
Smallpox Vaccine
Administration



JAMA 1999;281:1735-45

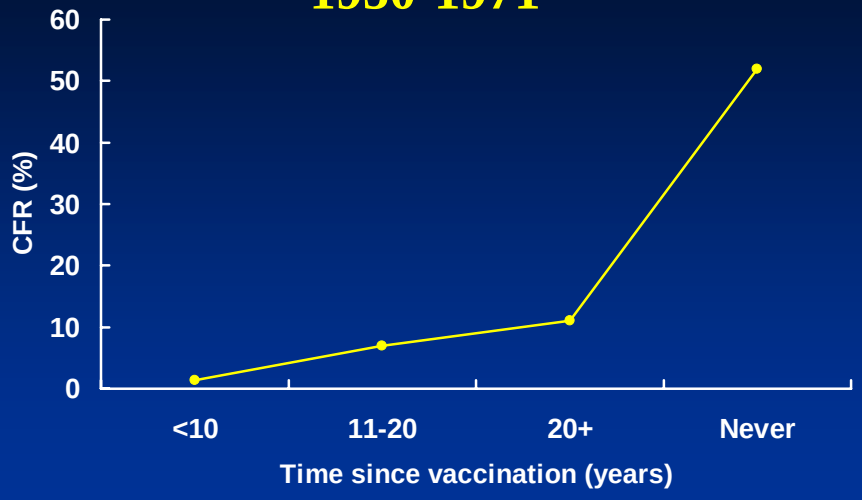
WHO

Primary Vaccination Site Reaction



SAINT LOUIS UNIVERSITY

CFR by Vaccination Status, Europe, 1950-1971



Mack TM. J Infect Dis 1972;125:161-9.

Vaccination and Immune Status

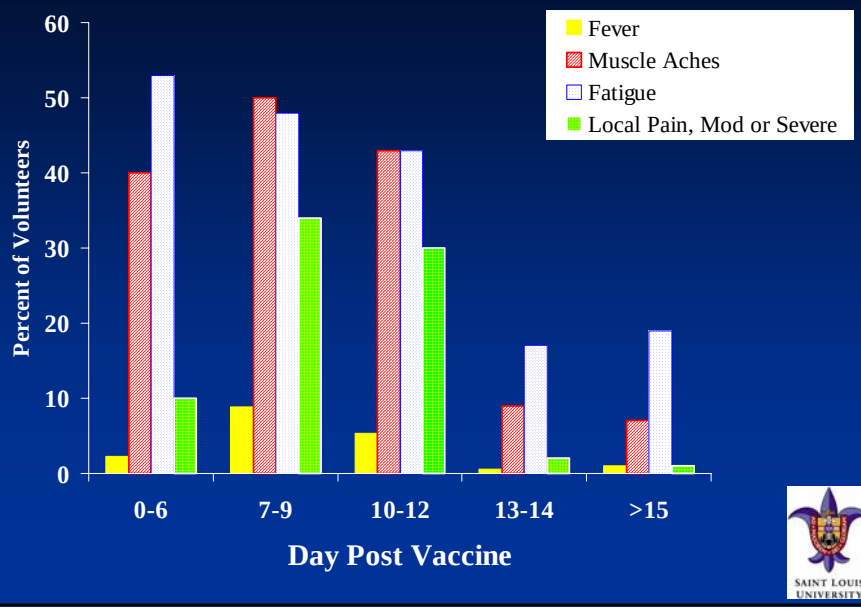
- High level of protection for 3 years following vaccination
- Duration of immunity is not clear; experience of naturally exposed persons never fully measured
- Neutralizing antibodies following single dose decline significantly over 5-10 years

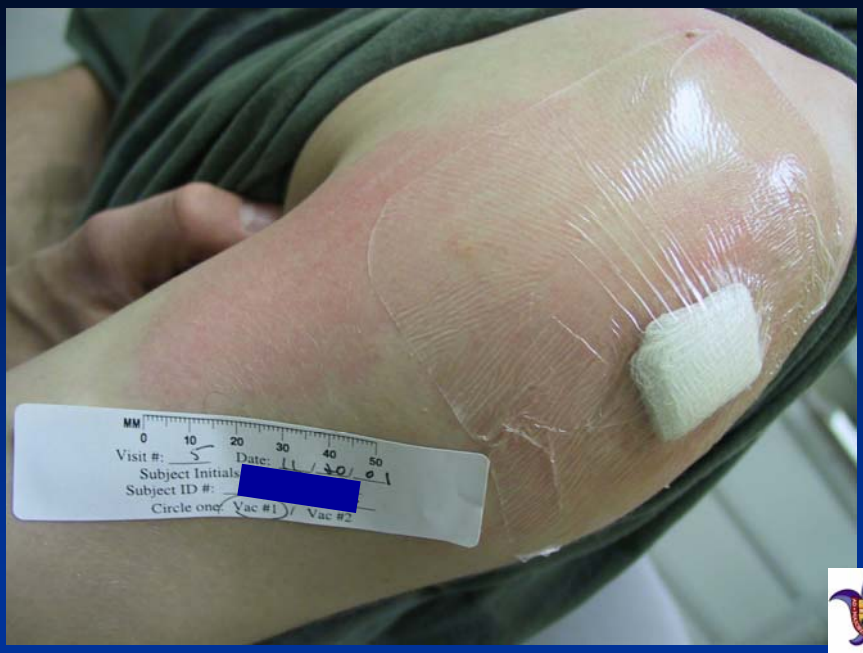
Smallpox Vaccination (1:5 Dilution)

Minor Side Effects On Days 7 - 9*

- Muscle aches 50%
- Fatigue 48%
- Headache 40%
- Nausea 14%
- Fever (>100 °F) 12%
- Pain at vaccination site: mild 43%, moderate 32%,
- Regional lymphadenopathy: mild 21%, moderate 5%

Acute Viral Illness Associated with Vaccinia



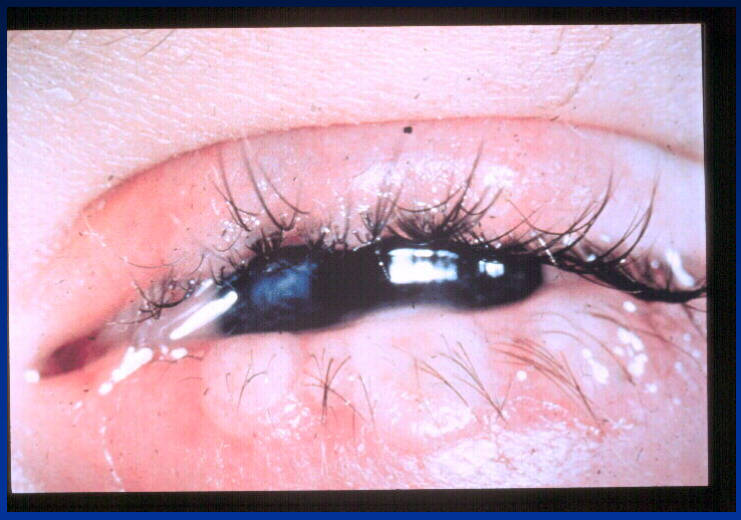


Contraindications for Vaccination

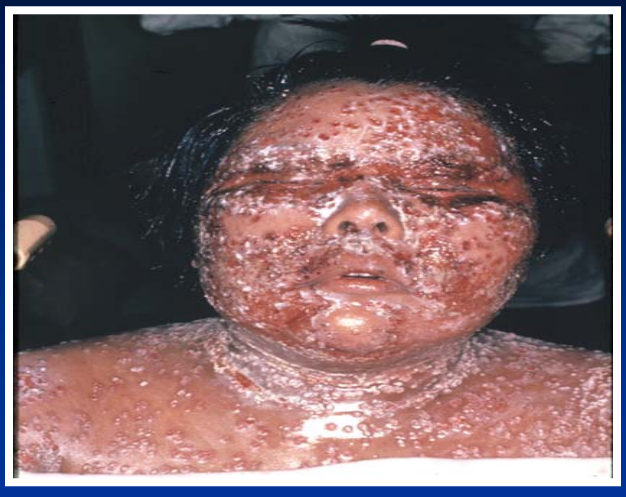
1. Immunodeficiency *
2. Allergies to polymyxin B, streptomycin, tetracycline, or neomycin
3. Eczema; including past history *
4. Pregnancy
5. Acute or chronic skin conditions (until resolved)

* Risk of accidental inoculation from household vaccinee's site

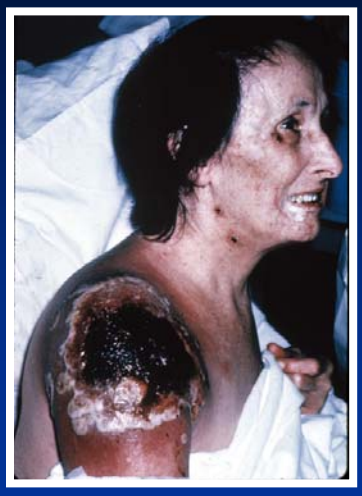
Ocular autoinoculation



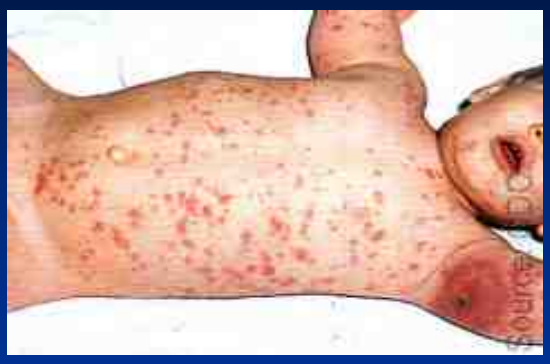
Eczema Vaccinatum



Progressive Vaccinia



Generalized Vaccinia



Adverse Reaction Rates*

Reaction	Primary Vaccination	Re - vaccination
Inadvertent inoculation	1/1,700	1/24,000
Generalized vaccinia	1/5,000	1/111,000
Eczema vaccinatum	1/26,000	1/333,000
Progressive vaccinia	1/667,000	1/333,000
Postvaccinial encephalitis	1/80,000	1/500,000
Death	1/million	0.25/million

*Adapted from CDC.. MMWR 2001;50(RR-10)

US Smallpox Vaccine Supply

- 15 million doses (Dryvax) now in stock
  - 1:5 dilution, 100% success rate in recent study
  - 1:10 dilution, 99% success rate
  - 100-dose vials
- 70-90 million additional doses of Aventis vaccine recently reported
- Contract with Acambis for ~ 220 million doses produced on cell culture media

Vaccine Immune Globulin

- Obtained from vaccinated donors
- Given with vaccine for persons at high risk for complications (pregnancy, eczema, HIV)
- Estimated 250/million vaccinees would require VIG for vaccine-related complications
  - Vaccinated soldier with HIV Rx'd with VIG and survived
- Current supplies very limited

Pre-Event Vaccination: Critical Considerations

- The risk of a smallpox terrorist attack is considered low, and population at risk cannot be determined
- Definite risk of serious adverse events; may be higher today due to large numbers of immuno-compromised
- Essential to ensure effective screening for vaccine contraindications, among both vaccinees and their contacts.

Pre-Event Smallpox Vaccination

- November 2001
  - CDC recommends against pre-event vaccination
- June 2002
  - ACIP recommendations for limited pre-event vaccination
- September-October 2002
  - ACIP expands recommendations to ~ 500,000 HCWs
- November 2002 - ?
  - Awaiting final federal decision

Pre- Event Vaccination

Pre-Vaccination of "first responders" who volunteer to care for the initial smallpox patients either through their normal course of work or their work responsibilities in time of an emergency – includes healthcare workers and smallpox response teams (*public health and law enforcement)*

Federal Smallpox Vaccination Policy Options (10/4/02)*

- Stage I – 500,000 public health response teams and health care workers at hospitals expected to receive smallpox patients
- Stage II – 10 million health care workers and first responders (police, fire, EMS)
- Stage III – Available for all citizens

"Those who forget history…" NYC Smallpox Outbreak of 1947

- April 1947: 12 cases of smallpox
- Mayor recommends that all 7.5 million New Yorkers be vaccinated
- Hospitals, clinics, schools, police stations, union halls designated as vaccination sites;
- ~ 1000 physicians and nurses staffed the clinics; ~ 3000 community volunteers

The New York Times FRIDAY, APRIL 18, 1947.

HALF MILLION HERE VACCINATED IN DAY

City's Drive Against Smallpox Pressed as Shortage of Vaccine Is Overcome

2,000,000 NOW IMMUNIZED

85 Police Stations Opened as Clinics—Death in Camden From Disease Reported

Half a million New Yorkers were vaccinated yesterday as a temporary shortage of vaccine, which was delaying the city's three-week program of protecting the population against smallpox, was overcome.

Dr. Israel Weinstein, health commissioner, estimated that 2,000,000 persons had been immunized during the campaign. With the receipt of 3,351,900 units of vaccine from pharmaceutical manufacturers, the 250 free public vaccination clinics in the city had adequate supplies.

The eighty-five police stations were opened for public vaccinations at noon, and at 10 P. M. they had cared for 119,486 persons. Some precincts had crowds of three or four times that number, long queues forming around the blocks.

Last Smallpox Outbreak in NYC - 1947

Public Health Response to Bioterrorism

- Detection of a potential outbreak
  - Rapid investigation to confirm that outbreak has occurred and identify etiology (natural vv intentional)
- Notification of key partners (*esp medical community)*
- Epidemiologic and criminal investigation
- Maintain active surveillance to track morbidity
- Implement control measures, as indicated
- Pro-active communication with public and providers

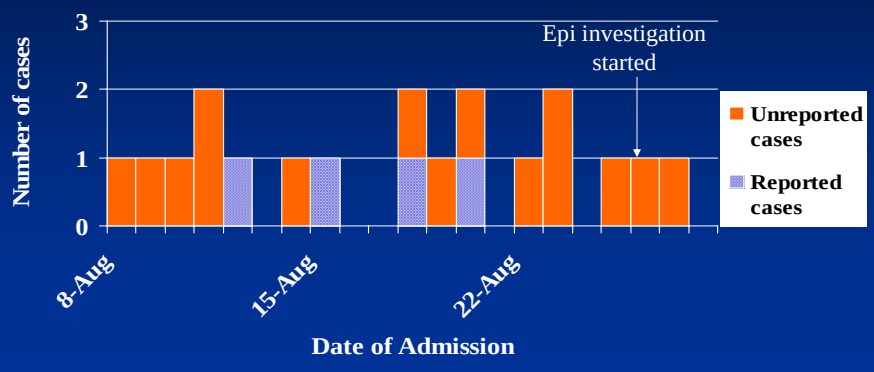
Surveillance Methods for Bioterrorism in NYC

- Traditional Surveillance via Provider Reporting
  - Enhance awareness of medical/lab communities
- Increase in unexplained infectious illnesses/deaths
  - ICU surveillance (*1º in response to high profile event)*
  - Death registry/Medical Examiner surveillance
- Syndromic Surveillance (*eg, influenza-like illness*)
  - 911
  - ER visits
  - Employee health
  - Pharmaceutical sales

Traditional Public Health Surveillance

- Medical care providers' *reporting* of:
  - Confirmed cases (clinical or lab)
  - Unusual diseases
  - Unusual patterns of illness
- Laboratorians' *reporting* of:
  - Laboratory-confirmed cases
  - Unusual clinical isolates
  - Unusual patterns of routine isolates

West Nile Virus 1999: The Power of Physician Reporting



Prevention

The best way to prevent a terrorist event from being an overwhelming disaster is to prevent it from happening in the first place:

- Strengthen and enforce the UN's Biologic and Chemical Weapons Conventions
- Restrict sale of BT organisms from lab repositories worldwide, as well as safeguard research stocks
- Enhance international intelligence capacity to identify terrorists working with WMD agents
- Address the global health and human rights issues (*social/political/economic factors*) that foster terrorism