

# Implications of Smallpox Immunization

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# Background

- September 11<sup>th</sup>, 2001
- Terrorists attack the World Trade Center and the Pentagon
- Homeland Security is high priority

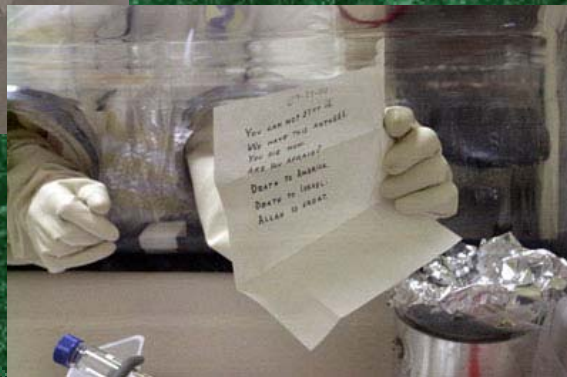


Thomas E. Franklin / The Record

# Background



- October 2001 U.S. Mail contaminated with anthrax is found in Senate office building and NBC
- Bioweapons become a reality to the American public
- February 2004—Senate office buildings closed after Ricin discovered



# Objectives

- Bioweapons
- Smallpox
- Smallpox vaccination
- Considerations prior to immunization

# Bioweapons

- Bioterrorism → intentional release of viruses, bacteria, or toxins for the purpose of harming or killing civilians
- Threat agents → Anthrax, Botulism, Plague, Smallpox, Tularemia, SEB, Ricin toxin, Brucella

# Bioweapons

- Characteristics that make organisms good agents for use as a weapon:
  - (1) accessibility to the organism and ease of production
  - (2) stability
  - (3) infectivity--infectious dose and route of infection
  - (4) effectiveness-- is it transmissible from person to person, morbidity, mortality

# Smallpox as a bioweapon

- accessibility to the organism and ease of production
- stability
- infectivity
- effectiveness
- CDC and Vektor Lab are only 2 approved sites of storage, likely others
- Isolated from scabs after 13 years
- Only a few virions to cause infection
- Highly infectious via respiratory droplets, 30% mortality rate, no treatment

# Smallpox as a bioweapon

- Smallpox was first used as a biological weapon during the French and Indian War of 1754-1767
- British soldiers distributed blankets that had been used by people infected with smallpox
- >50% of tribe members died

# Smallpox

- The WHO declared smallpox eradicated in 1980. The last endemic case was in Somalia in October of 1977
- Routine immunization was discontinued in the U.S. in 1972

# The Virus

- **Variola Virus**--family Poxviridae, sub-family Chordopoxvirinae, and the genus orthopoxvirus
- one linear double-stranded DNA molecule of 130-375-kb
- replicates in the cytoplasm of the infected cell
- shaped liked bricks when viewed by electron microscopy
- diameter of 200nm



# Pathogenesis

- Enters through the respiratory mucosa → infects macrophages
- The macrophages migrate to lymph nodes
- Viral replication → asymptomatic viremia, 3-4<sup>th</sup> day
- Replication continues in the reticuloendothelium system, 4-14 days
- Second viremia → virus infecting mucous membranes of the mouth and pharynx

# Pathogenesis

- Leukocytes infected with the virus invade the capillary epithelium in the dermal layer of skin → rash
- The oropharyngeal and skin lesions contain abundant quantities of virus
- Spreads by respiratory droplet or aerosol to next human host

# Clinical Presentation

- incubation period → 7-17 days, usually 10-12 days
- prodrome → 2-3 days, abrupt onset
  - severe headache
  - backache
  - malaise
  - fever greater than 101 degrees
  - Abdominal pain and vomiting
  - delirium
- lesions in the mouth and oropharynx precedes the rash by about 1 day

# Rash



# 5 Types of smallpox

- **Variola major** → 90% of the cases, 30% fatal
- **Modified** → lesions are fewer, smaller, and more superficial is rarely fatal. More common in immunized patients.
- **Flat-type** → lesions are flat, develop more slowly, and coalesce. It accounted for 7% of cases and was 97% fatal.
- **Hemorrhagic** → 3% of cases, >99% fatal, extensive bleeding into the skin, mucous membranes, and gastrointestinal tract.
- **Variola sine eruptione** → mild occurs in vaccinated contacts or infants with maternal antibodies.

# Diagnosis

- If suspect smallpox immediately isolate patient in a negative pressure room
- Send samples of vesicle material to CDC for EM, PCR, and viral culture
- Send serum sample to CDC for serology
- Differential diagnosis of generalized rash illness

**TABLE 2. DIFFERENTIAL DIAGNOSIS OF SMALLPOX AND CHICKENPOX.**

DIAGNOSTIC CRITERIA	SMALLPOX	CHICKENPOX
History		
Recent contact with smallpox	Yes	No
Recent contact with chickenpox	No	Yes
Prior vaccination against smallpox*	In some cases	In some cases
Prior vaccination against chickenpox	In some cases	No
Incubation period (days)	10-12 (range, 7-17)	14-16
Prodromal phase†		
Duration (days)	2-4	0-2
Fever	Yes	In some cases
Headache, backache	Yes	In many cases
Muscle pain, malaise	Yes	In some cases
Pallor, transient rash	In some cases	No
Physical examination		
Scar from smallpox vaccination*	In some cases	In some cases
Skin lesions†		
Distribution	Centrifugal	Central
Peak (days after onset of eruption)	7-10	3-5
Evolution	Same stage	Different stages
Diameter (mm)	4-6	2-4
Shape	Round	Oval
Depth	Deep	Superficial
Desquamation (days after onset of eruption)	14-21	6-14
Lesions on palms and soles	Common	Uncommon
Complications		
Skin infection	In some cases	In some cases
Facial scarring	In most cases	In some cases (superficial)
Pneumonia	In some cases	Rare
Blindness	In some cases	No
Encephalitis	In some cases	Rare
Case-fatality rate (%)		
Chickenpox	—	<1 (2-3/100,000)
<i>Variola major</i>	30	—
<i>V. minor</i>	<1	—
Laboratory diagnosis		
Antigen or nucleic acid detection	Variola virus	Varicella-zoster virus
Electron-microscopical findings	Poxvirus particles	Herpesvirus
Results of culture on chorioallantois	Characteristic pocks	No growth
Serologic findings	Increase in antibody to orthopoxvirus	Increase in antibody to varicella virus

\*Routine vaccination against smallpox stopped in 1972 in the United States and in the early 1980s in other countries, except in the case of laboratory personnel working with orthopoxviruses. The vaccination scar may fade with time.

†Patients who have undergone smallpox vaccination may have attenuated disease.

# Treatment

- No specific treatment
- Supportive care
- Prevent spread of virus
  - Vaccination within 2-3 days of exposure will provide almost complete protection from disease
  - Vaccination within 4-5 days will decrease fatal illness

# Outcomes

- Fatality rate of 30%
- Death from septic shock
  - Circulating immune complexes
  - Soluble variola antigens
- 65-80% of survivors have pockmarks
- 1% of patients with panopthalmitis develop blindness

# Spread of smallpox today

- Epidemiological modeling determined the  $R_0$  for industrialized countries to be 4-6, but initially would likely be 10-12 until proper identification of smallpox is made
  - Gani R, Leach S. *Nature*. 2001;414:748-751
- If there were a smallpox release in the United States that put 50% of the population at risk the expected number of deaths would be 100,000 to 1 million
  - Bicknell WJ. *NEJM* 2002;346(17):1323-24

# Smallpox Vaccination

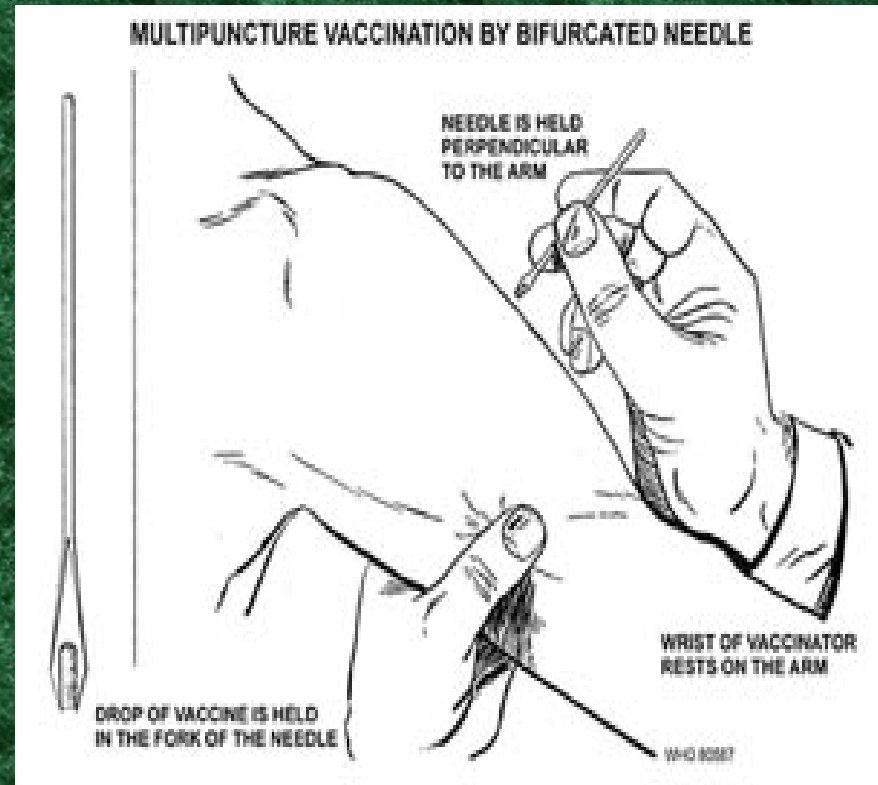


- Dr. Edward Jenner  
1796—1<sup>st</sup> vaccine
- Live virus vaccine
- Produced by  
scarification of calves



# Vaccine Administration

- Bifurcated needle
- Intradermal
- Contraindicated
  - Pregnancy
  - Atopic dermatitis
  - Immunocompromised
  - Allergy to: polymyxin B, streptomycin, chlortetracycline, neomycin



# Vaccine Reaction

## Smallpox vaccination site Days 4 through 21



Day 4



Day 7



Day 14



Day 21

# Immunity

- >95% have detectable neutralizing Ab at a titer  $\geq$  1:10 within 1-2 weeks
  - Fulginiti VA et al. Clinical Infectious Diseases. 2003; 37(2):241-50
- Neutralizing Ab at a titer of 1:10 in 75% of persons up to 10 years after second dose of vaccine
  - Cherry JD et al. Journal Infectious Diseases. 1977;135:145-54
- fatality rate for smallpox
  - 1.3% if vaccine <10 years prior
  - 11% if vaccine >20 years prior
  - The fatality rate for unimmunized individuals was 52%

# Vaccine Supply

- Dryvax--15 million doses
- Frozen vaccine--70-90 million doses
- Fall short if large epidemic were to occur

# Vaccine Supply

- Randomized, double-blind trial
- 60 adults with no previous smallpox immunization were vaccinated
- Clinical success—primary endpoint
  - 95% with undiluted vaccine
  - 70% with a 1:10 dilution
  - 15% with 1:100 dilution

Frey SE, Newman FK, Cruz J, et al. NEJM 2002;346(17):1275-80

# Vaccine Supply

- Randomized single-blind trial
- 680 adults, no previous smallpox immunization
- Clinical success—primary endpoint
  - 97.2% with undiluted vaccine
  - 97.1% with 1:10 dilution

Frey SE, Couch RB, Tacket CO, et al. NEJM  
2002;346(17):1256-74

# Complications

- Non-serious reactions:
  - moderate or severe local pain and erythema
  - Regional lymphadenopathy
  - temperature of at least 100 degrees
  - severe headache
  - moderate to severe myalgias
  - chills
  - nausea
  - fatigue

# Complications

- **Postvaccinial encephalitis:**
  - 8-15 days after vaccination
  - fever, headache, vomiting and drowsiness
  - meningitic signs, spastic paralysis, seizures, coma
  - vaccinia immune globulin (VIG) –no benefit

# Complications

- **Progressive vaccinia: vaccinia gangrenosa or vaccinia necrosum**
  - progressive necrosis at the site of inoculation
  - similar foci of infection will appear at other sites on the body
  - necrosis of the tissues, osteomyelitis, and associated bacterial superinfection
  - Treat with **VIG**



# Complications

- **Eczema vaccinatum:**
  - Individuals with active eczema or a history of eczema, atopic dermatitis are at risk
  - Extensive vaccinia eruptions at sites of active or prior dermatitis, lymphadenopathy
  - Treat with **VIG**



# Complications

- **Generalized Vaccinia:**
  - secondary eruption of the vaccinia rash at a remote site
  - 6-9 days after vaccination
  - Treat with **VIG** in severe cases
- **Inadvertent inoculation:**
  - autoinoculation of vaccinia virus to a secondary site
  - common sites include the face, eyelids, nose, mouth, genitalia
  - Treat with **VIG** if ocular or periocular implantation

# Complications

- **Vaccinia keratitis:**
  - eye pain, photophobia, tearing, and blurred vision
  - corneal scarring, visual impairment or blindness
  - **VIG is contraindicated**
- **Other rashes:**
  - typically are flat, erythematous, macular or urticarial
  - erythema multiforme, Stevens-Johnson Syndrome, roseola vaccinia, toxic erythema, and post-vaccinial urticaria
- **Fetal vaccinia:**
  - results in stillbirth or death shortly after delivery
  - extensive skin lesions on the infant

# Complications

- **Myopericarditis:**
  - Halsell JS, et al. JAMA 2003;289(24):3283-89
  - reported 18 cases among US military service members from December 2002 through March of 2003
  - chest pain, malaise, and fever
- **Acute Ischemic Events:**
  - CDC is investigating myocardial ischemic events
  - A MI was reported to the CDC in April of 2003
- **Death:**
  - usually the result of progressive vaccinia or postvaccinial encephalitis
  - Historically it is rare with 1 to 2 deaths per million primary vaccinations

**Table 2.**

*Occurrence of complications\* of smallpox (vaccinia) vaccination: 1960s to 2003.*

Complication	Occurrence				
	US 1960s–1970s (Frequency per 1 Million Vaccineses) <sup>14-16</sup>	2001–2002 US Dilutional Studies (First Dose of Vaccine; N=680) (Prescreening <sup>17</sup> )	2002 Israeli Experience (N=929) (Pre- screening <sup>18</sup> )	December 2002–Ongoing US Phase 1 Pre- Event Smallpox Vaccination Plan <sup>13,19-21,24</sup>	
				Military (N=Approximately 325,000 as of May 16, 2003) (Prescreening <sup>5</sup> )	Civilian (N=23,845 as of March 21, 2003) (Prescreening <sup>11</sup> )
<b>Nonserious reactions (local and systemic)</b>	NA			NA	413 cases
1. Moderate or severe local pain and erythema		1. 33.8%	1. NA		
2. Regional lymphadenopathy		2. 30.5%	2. NA		
3. Temperature of $\geq 37.8^{\circ}\text{C}$ ( $\geq 100^{\circ}\text{F}$ )		3. 8.9%	3. 5%		
4. Severe headaches		4. 2.1%	4. 26% (severity unknown)		
5. Moderate to severe muscle aches		5. 20.6%	5. 18%		
6. Chills/shivering		6. 6.5%	6. 9%		
7. Nausea		7. 3.9%	7. 12%		
8. Fatigue		8. 19.7%	8. 31%		
<b>Robust take</b>	Common	10%	NA	NA	NA
<b>Serious reactions</b>					
Postvaccinial encephalitis	3 cases (primary vaccinees), 2 cases (revaccinees)	None	1 case	1 case	None
Progressive vaccinia (vaccinia gangrenosa, vaccinia necrosum)	2 cases (primary vaccinees), 3 cases (revaccinees)	None	None	None	None
Eczema vaccinatum	11 cases (primary vaccinees)	None	None	None	None
Generalized vaccinia	24 cases (overall)	None	None	36 cases	8 cases
Inadvertent inoculation (accidental implantation)	25 cases (overall)	None	None	48 cases	2 cases (ocular), 28 cases (nonocular)
Vaccinia keratitis	Rare	None	None	NA	None
Other rash (eg, erythema multiforme, Stevens-Johnson Syndrome, roseola vaccinia, toxic erythema, and postvaccinial urticaria)	NA; serious rashes were rare	14.3%	None	NA	None
Fetal vaccinia	Rare (<50 cases)	None	None	NA	None
Myopericarditis	NA	None	NA	26 probable cases; 1 confirmed case	2 cases (primary vaccinees)
Cardiac ischemic events	NA	None	NA	1 case <sup>3</sup> (unknown previous vaccination status)	5 cases <sup>2</sup> (2 primary vaccinees, others unknown previous vaccination status)
Other serious reactions	NA	12 cases <sup>**</sup>	None	NA	37 cases <sup>**</sup>
Death	1 (overall)	None	None	None attributed	2 deaths caused by myocardial infarctions <sup>**</sup>

# Treatment

- **VIG: Vaccinia Immune Globulin**
  - no randomized control studies
  - isotonic sterile solution of immunoglobulin fraction of pooled plasma from individuals vaccinated with vaccinia
  - Available for the CDC

# Treatment

- **Antivirals:**
  - **methisazone** --inhibits replication of vaccinia, used in 1950's
  - **Ribavirin**-- in addition to VIG was used to treat progressive vaccinia is a 67-year-old man with metastatic melanoma and chronic lymphocytic leukemia. He had received a vaccinia melanoma oncolysate vaccination. Kesson et al Clinical Infectious Diseases. 1997;25:911-4
  - **Cidofovir**--animal studies have shown it to be lethal to orthopoxvirus infections. Cidofovir plus VIG eliminated vaccinia infection in immunodeficient mice. Bray, M et al. Clinical Infectious Diseases. 2003;36:766-774.

# Pre-event Smallpox Immunization

- Phase 1: Immunization of select armed forces personnel, US Department of State employees serving over-seas, and members of public health response and health care teams.
- Phase 2: Immunization of other medical providers and first responders.
- Phase 3: Vaccination offered to the general public.

# Implementing Pre-event Immunization

- Safety of employees and patients
- liability for vaccine complications and compensation
- perceived threat of a biological terrorism attack and concern for personal safety

# Safety

- **Contact vaccinia:** transmission of vaccinia virus to an unimmunized person
- Expected to have 2-6 cases per 100,000 primary vaccines, per 1960's data
- Today consider →
  - large proportion of the population who is non-immune
  - prevalence of atopic dermatitis in children has increased from 3%-6% to 6%-22%
  - solid organ transplantation, advances in oncology, HIV and AIDS

# Safety

- New York State hospital discharge file for 2001
- High Risk--primary or secondary diagnoses that are considered contraindications to immunization
- Lower Risk--diagnoses suggestive of an immunocompromised state
- NYC 21% had diagnoses for high-risk conditions and 36% for lower risk
- In the remainder of New York the percentages of at risk discharges were 19 and 36% respectively
- at any one point in time greater than 50% of inpatients have 1 or more conditions that put them at higher risk

Smith PF and Sepkowitz KA. JAMA 2003;289(12):1512-13

# Liability

- **Section 304 of the Homeland Security Act:**
  - enacted on January 4<sup>th</sup> 2003
  - protects manufactures and those health care entities that would administer the vaccine
  - removes liability from immunized individuals who inadvertently inoculate others, including health care workers
  - covers injury and death attributable to the vaccine, vaccinia immune globulin, and any other substance used to treat or prevent smallpox

# Liability

- **US Department of Health and Human Services-- federal compensation package**
  - Signed into law in April of 2003
  - no-fault fund is as follows
    - (1) Those who are permanently and totally disabled could get up to \$50,000 a year until they reach retirement age and transfer to a regular retirement plan
    - (2) Those less injured could get the same annual benefit but with lifetime maximum of \$262,000
    - (3) For those who die as a result of vaccination, a lump sum payment of \$262,000 would be paid to the surviving spouse
    - (4) A surviving spouse with children could choose between the payment option in number 3 or up to \$50,000 annually until the children turn 18
    - (5) Those dissatisfied with their award could sue under the Federal Tort Claims Act

# Individual Attitudes

- Kwon N, et al. *Academic Emergency Medicine*. 2003;10(6):599-605.
- 23 multiple-choice question survey to emergency department attendings and residents
- 42 programs provided responses
- 43.4% of individuals would volunteer
- Factors which made willingness to undergo vaccination more likely included
  - previous vaccination 1.46 times more likely
  - perceived risk of a bioterrorist attack 2.7 times more likely
  - perception of the lack of risk for complications from vaccination

# Individual Attitudes

- **Everett WE, et al Academic Emergency Medicine. 2003;10(6):606-11**
- survey of the largest adult and pediatric academic emergency departments in the 10 largest U.S. cities
- physicians, mid-level practitioners, and nurses
- 43% response rate
- 73% of respondents were willing to receive smallpox vaccine under pre-event plans
- Self-protection was the most common reason given for willingness to be vaccinated (72%)

# Conclusion

- Smallpox was eradicated by a successful vaccination and containment campaign
- Emergence as a biological threat agent would be a public health disaster
- Smallpox vaccination has many risks to the individual vaccinated and those inadvertently exposed
- Vaccination protocols, treatment guidelines and hospital policy should be in place prior to initiation of immunization