A Rash Overview of the Cutaneous Manifestations of Agents of Bioterrorism

Boris D. Lushniak, MD, MPH
RADM, Asst Surgeon General USPHS
Asst Commissioner, Counterterrorism Policy FDA

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DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

A Rash Overview of the Cutaneous Manifestations of Agents of Bioterrorism
NASA 2008 Occupational Health Conference
Boris D. Lushniak, MD, MPH

- No relationship with commercial supporters
- No off-label discussion of drugs or devices
- Federal government employee
- Work supported by US Government

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A Rash Overview

- A skin eruption
- Outbreak of activities in a brief period
- Quick in producing an effect
- Marked by ill-considered boldness or haste

  - Webster's II Dictionary

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Outline

- Overview of bioterrorism (BT)
- Review and update on BT agents with skin manifestations
  - Emphasis on anthrax and smallpox
- Your role in preparedness and response

Learning Objectives

- Identify the bioterrorist agents that have cutaneous manifestations
- Recognize the cutaneous findings and other health effects associated with potential bioterrorist agents
- Define your potential role in the event of a bioterrorist event

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My Secret Objective

Always exciting to hear a doctor say,
"Dear God what the hell is that?"

David Letterman
6/10/2003
Top Ten List
RE Monkeypox

Bioterrorism

Intentional or threatened use of viruses, bacteria, fungi, or toxins from living organisms to produce death or disease in humans, animals, or plants

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History

- 1346 - Plague in Kaffa (Feodosia) in Crimea
  - Siege of the Genoans by Tartars
  - Catapulting of corpses
- 1763 – French and Indian War
  - Smallpox tainted blankets from British to the Indians

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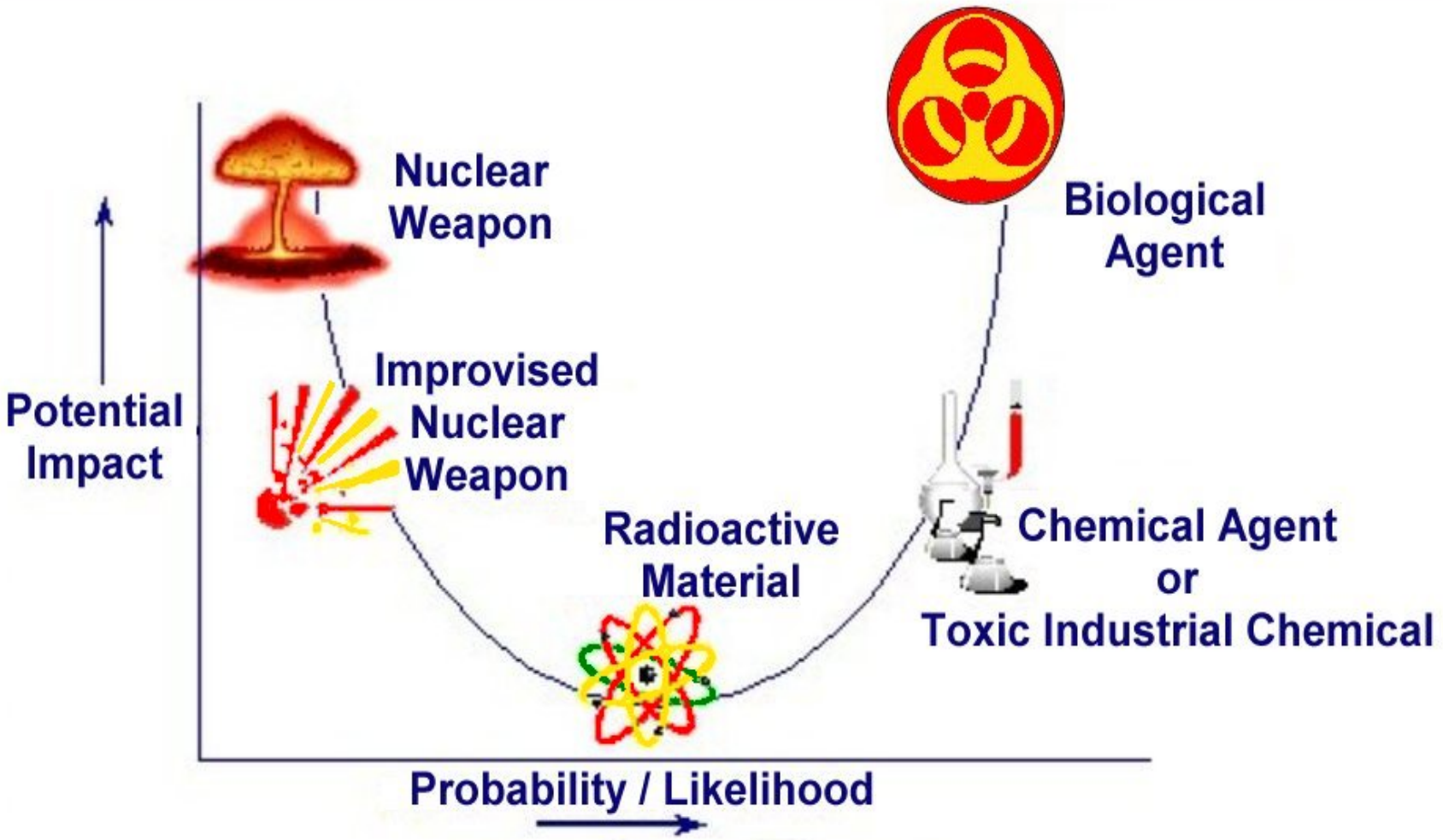
PROBABILITY vs. IMPACT



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Biologics as Weapons and Threats

- History of development for bioweapons
- Easy to obtain, inexpensive to produce
- Potential for dissemination over large areas
- Organisms fairly stable in environment
- Potential high morbidity and mortality
- Person-to-person transmission (smallpox, plague, VHF)
- Difficult to diagnose and/or treat
- Can overwhelm medical services
- Perpetrators escape easily

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Biological Agents of Highest Concern (Category A)

- ***Bacillus anthracis* (Anthrax) ***
- ***Variola major* (Smallpox) ***
- ***Yersinia pestis* (Plague) ***
- ***Francisella tularensis* (Tularemia) ***
- **Filoviruses and Arenaviruses (Viral Hemorrhagic Fevers) ***
- **Botulinum toxin (Botulism)**
- **ALL suspected or confirmed cases should be reported to health authorities immediately**

* Cutaneous manifestations

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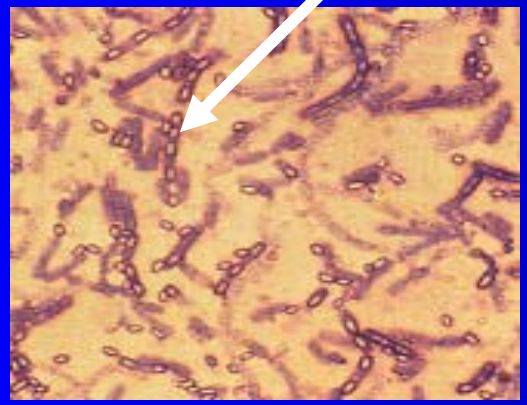
Anthrax

- Zoonotic disease in herbivores (e.g., sheep, goats, cattle) follows ingestion of spores in soil
- Three clinical forms
  - Cutaneous, Inhalational, Gastrointestinal
- *Bacillus anthracis* -- Gram-positive, spore-forming, non-motile bacillus



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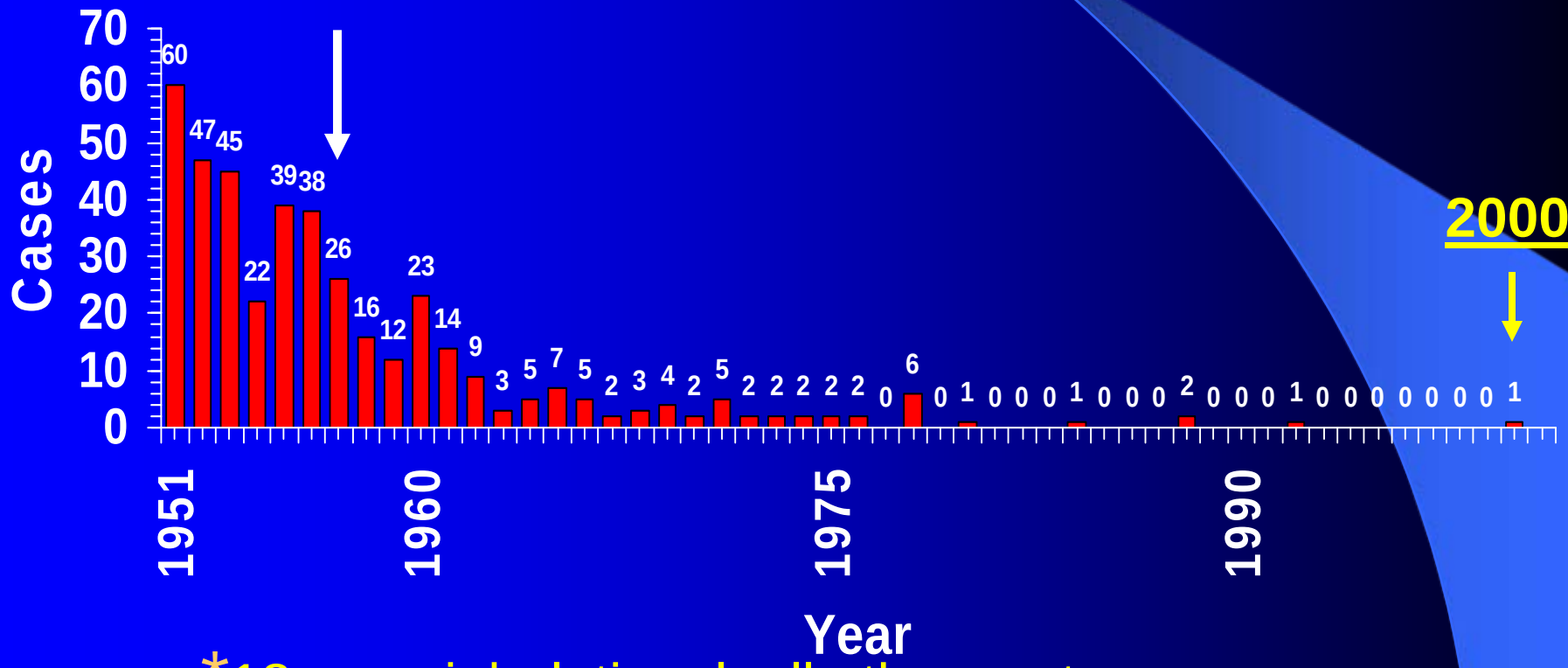
Cases of Anthrax in Humans U.S. 1951–2000* (N = 409)

Animal (Stern's) vaccination started in 1957.
Recommended for use in animals in endemic areas thereafter.



*18 were inhalational; all others cutaneous

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Anthrax: Current Issues

- Anthrax remains an endemic public health threat through annual epizootics
  - Farm workers exposed to infected animals
  - Industrial processing of wool, hair, hides, or bones
    - 158 of 236 (67%) of cases in US from 1955-1999
    - 148 of 158 (94%) were cutaneous cases
  - Laboratorians with contact to spores

MMWR March 17, 2006 55(10); 280-282

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Anthrax: Current Issues

- *B. anthracis* is one of the most important pathogens on the list of bioterrorism threats
- Aerosolized stable spore form
- Human LD50 8,000 to 40,000 spores, or one deep breath at site of release

Inhalational Human Anthrax

- Extremely rare in United States
- Feb 2006 single case associated with dried animal skins (NY, PA)
- Incubation period: 1–7 days (up to 42 days?)
- Case fatality (prior to 2001):
  - Without antibiotic treatment--97%
  - With antibiotic treatment--75%
- Production of toxins made up of 3 proteins
  - Protective antigen, edema factor, and lethal factor
  - Toxins do not respond to antibiotics

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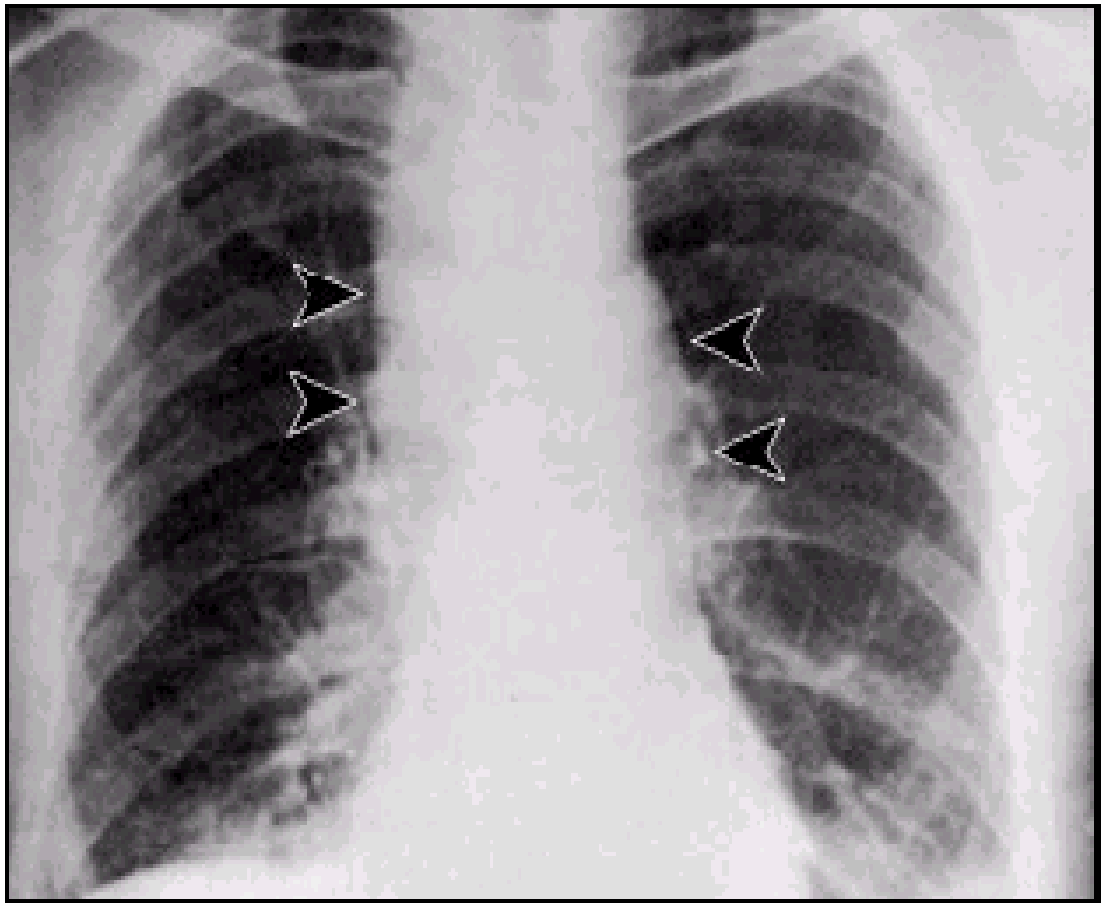
Inhalational Human Anthrax

- A brief prodrome -- “viral-like” illness
  - Myalgia, fatigue, fever, with or without respiratory symptoms
- Followed by hypoxia and dyspnea
  - Often with radiographic evidence of mediastinal widening
- Meningitis

Anthrax: Inhalational



Mediastinal widening

JAMA 1999;281:1735–1745

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Cutaneous Anthrax

- Form most commonly encountered in naturally occurring cases
- Incubation period: 1–12 days
- Case-fatality:
  - Without antibiotic treatment—20%
  - With antibiotic treatment—1%

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Cutaneous Anthrax
Clinical Progression

- Begins as non-tender pruritic macule then a papule
- Progresses into a vesicle or bulla (24-48 hours)
- Bulla 1-2 cm ruptures (satellite vesicles and edema)
- Depressed black necrotic ulcer (jet black eschar) with raised border and erythematous plaque
- Edema, erythema or necrosis without ulceration may occur
- Minimal scarring

Cutaneous Anthrax
Clinical Progression

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Anthrax

Roche et al. *New Engl J Med*. 11/6/2001 on-line.

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Brown recluse spider bite reaction

Ecthyma gangrenosum

(p. aeruginosa)

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Tularemia

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Staphylococcal wound infection

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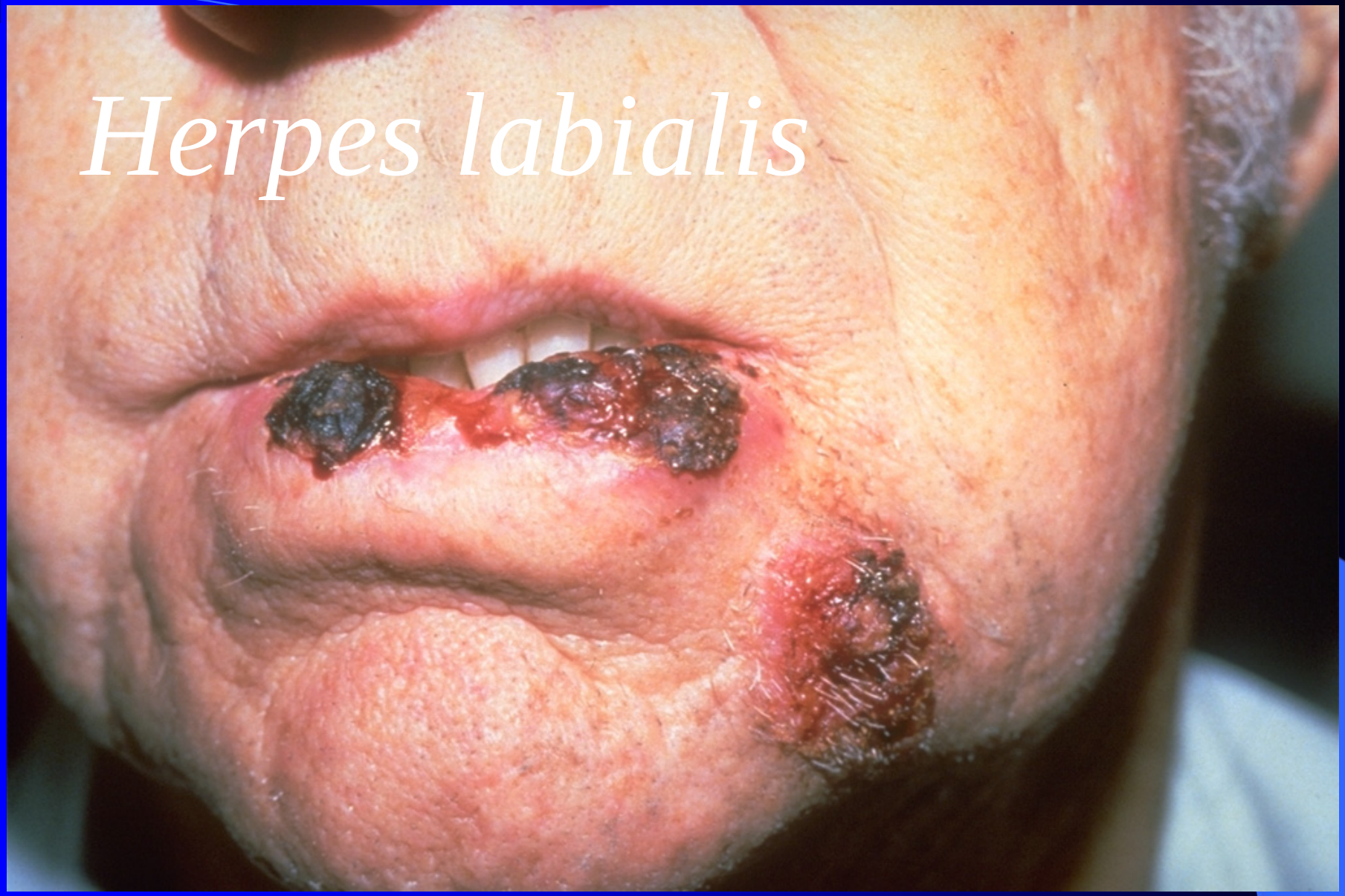
Herpes labialis



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Anthrax Response 2001

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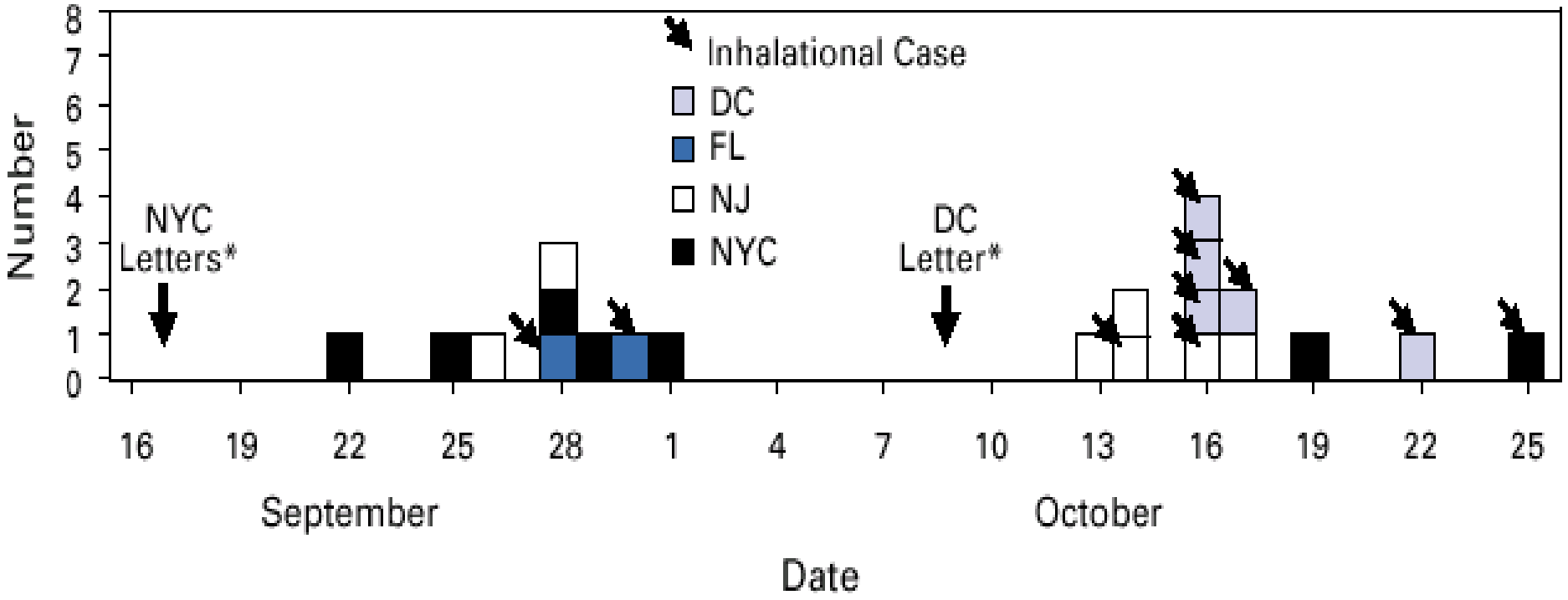
FIGURE 1. Number of bioterrorism-related anthrax cases, by date of onset and work location — District of Columbia (DC), Florida (FL), New Jersey (NJ), and New York City (NYC), September 16–October 25, 2001



* Postmarked date of known contaminated letters.

MMWR 50:44 Nov 9, 2001

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Anthrax, U.S.
October 4-November 19, 2001

- 11 inhalational, 11 cutaneous
- 5 deaths (all inhalational)
- 20 exposed to worksites where contaminated mail processed or received
- Post-exposure chemoprophylaxis initiated for 32,000 media, government, and mail workers (full course recommended for 10,300)

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Anthrax, U.S.
October 4-November 19, 2001

	FL	NYC	DC MD VA	NJ PA	CT
Cutaneous	0	7	0	4	0
Inhalational	2	1	5	2	1

Cutaneous Anthrax 2001 Summary

- 11 cases (7 confirmed, 4 suspect)
- 1 additional case in lab worker
- 6 males and 6 females
- 7 months to 54 years
- Sites
  - Head
  - Neck
  - Upper extremities

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Anthrax -- Diagnosis

Cutaneous

- Gram stain, polymerase chain reaction (PCR), or culture of vesicular fluid, exudate, or eschar
- Blood culture if systemic symptoms present
- Biopsy for immunohistochemistry, especially if person taking antimicrobials

Cutaneous Anthrax Treatment Protocol* for Cases Associated with Bioterrorist Events

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

**Ciprofloxacin not to exceed 1 gram daily in children. ◆60-day duration is to prevent inhalational anthrax.

Patient information sheets at www.bt.cdc.gov

*Source MMWR 2001;50:909–19

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Anthrax *Vaccine*

- Anthrax Vaccine Adsorbed
- Induces immunity to protective antigen
- 6-dose series (0-2-4 wks, 6-12-18 mos, qy)
- Over 600,000 doses to US military
- Some controversy -- but, studied by Institute of Medicine and approved by FDA
- Supplies are limited

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Smallpox – Variola

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Genus Orthopoxvirus
Family Poxviridae

- Double stranded DNA viruses
- Cytoplasmic replication (not in nucleus)
- Can cause human disease
  - Variola (smallpox)
  - Vaccinia
  - Cowpox
  - Monkeypox

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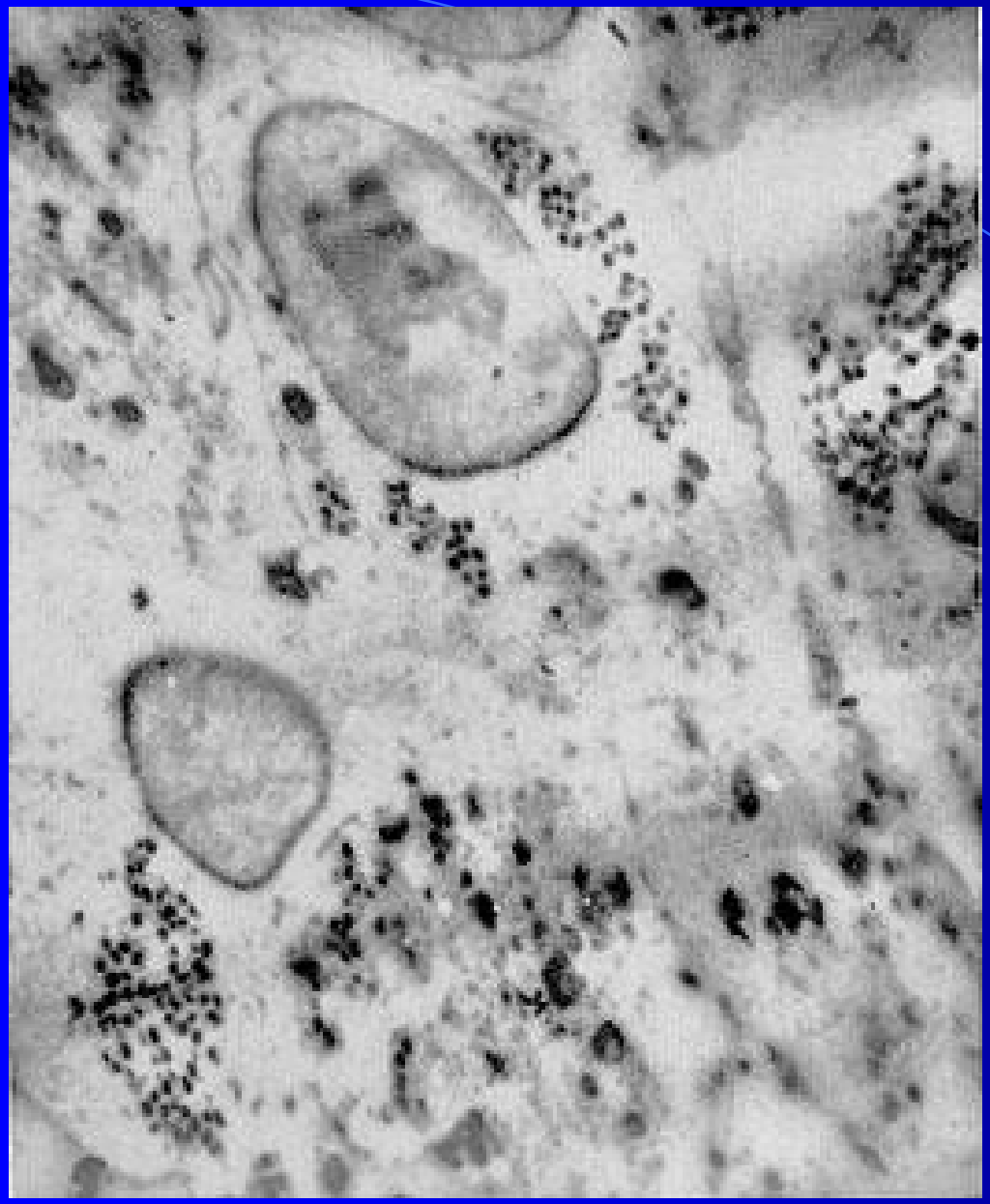
200 micron virions



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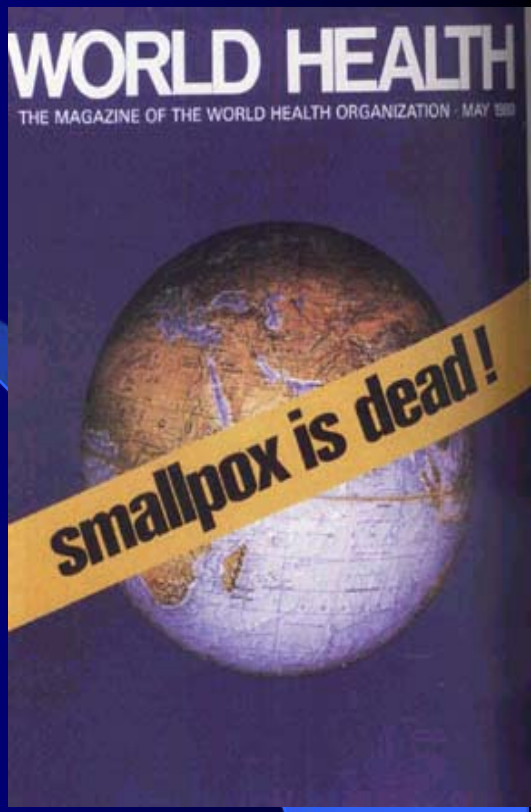
Smallpox History

- Known in Egypt and India - 3000 years
- 1796 – Jenner's cowpox vaccine
- 1949 – last US case
- 1950s -- 50 million cases/year
- 1967 – 10-15 million cases/year
  - 60% of world still threatened
- 1972 – vaccinations stopped in US
- 1977 – last natural case (Somalia)
- 1980 – WHO declares smallpox eradicated
- Virus remains stored at CDC and in Russia
- Impact in 20th century – 500 million deaths



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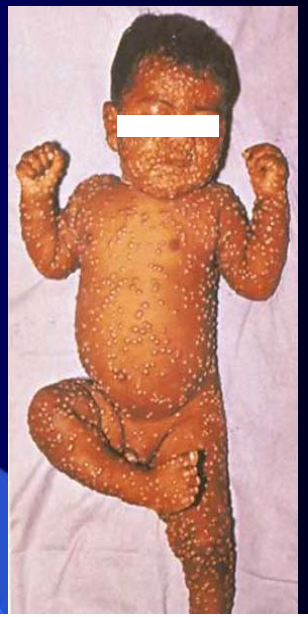
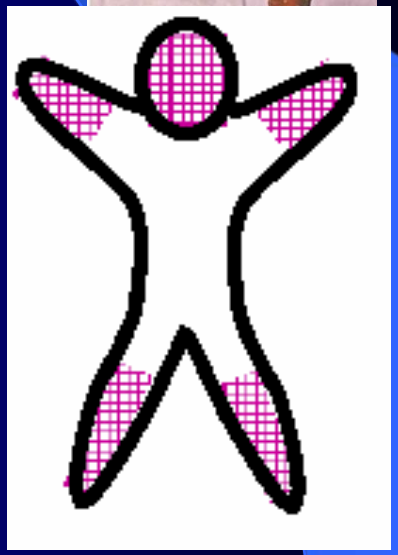
Smallpox

- Highly stable virus
- Infectious by direct contact/aerosol (usually within 6 feet)
- 30% of close contacts infected
- Infrequent indirect transmission (fomites such as bedding or clothing)
- Two clinical forms
  - Variola major – severe form, case-fatality >30%
  - Variola minor – less severe, case-fatality < 1%

Smallpox
Clinical Stages

- Incubation - 7-17 days
  - non-infectious
- Prodrome - lasts 2-4 days
  - **High fever (101-104)**, prostration, myalgias, malaise
  - Enanthem (now infectious) – small red macules and papules on tongue and mouth which ulcerate
- Exanthem
  - Centrifugal (face, arms/legs, hands/feet)
  - Progression -- macule-papule-vesicle-pustules-crust





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Smallpox
Lesion Progression

- Day 0-1 - Macule
- Day 2-3 - Papule
- Day 3-5 - Deep, tense vesicle often umbilicated
- Day 6-12- Deep, round, tense pustules
  - (like BB pellet embedded in the skin)
- Day 13-20 - Crusts
- Day 21-28 - Crusts separate
- Long-term - Depressed scars

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Variola Major
Clinical Presentations

- Ordinary smallpox
  - Discrete 60%
  - Semi-confluent/Confluent 30%
- Flat 6%
- Hemorrhagic 3%
- Modified (mild in vaccinated) rare

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Smallpox *Progression*

WHO. I. Arita.

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Smallpox
Clinical Forms

- Ordinary smallpox
  - 3% fatal with vaccination
  - 30% fatal without

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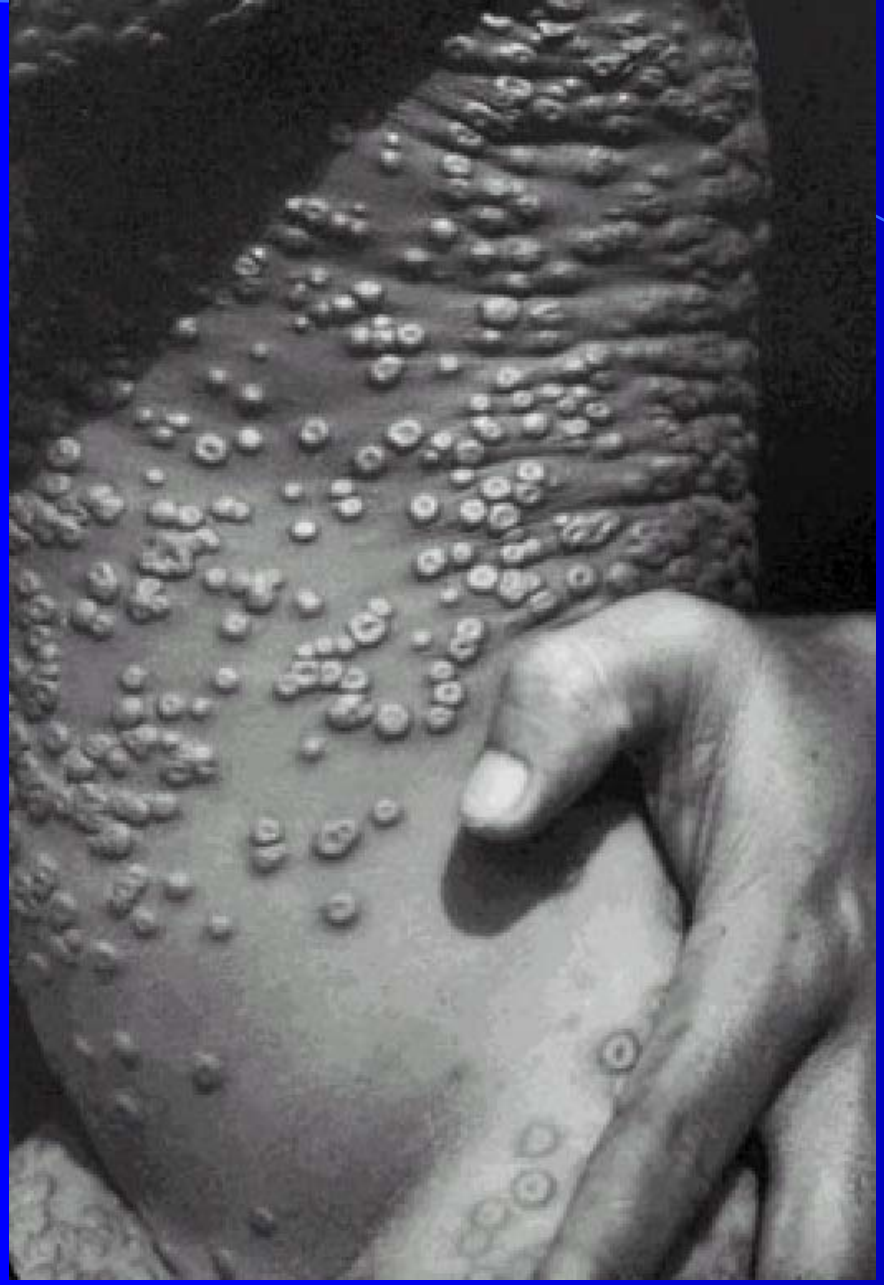

Ordinary Smallpox

Umbilicated Vesicles

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Varicella

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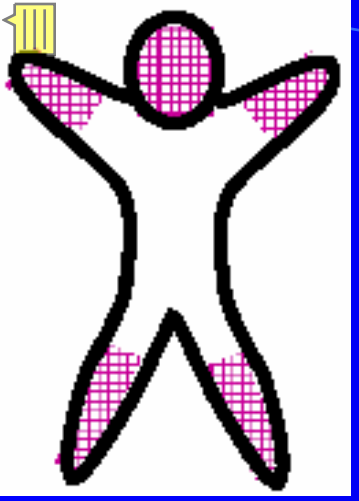
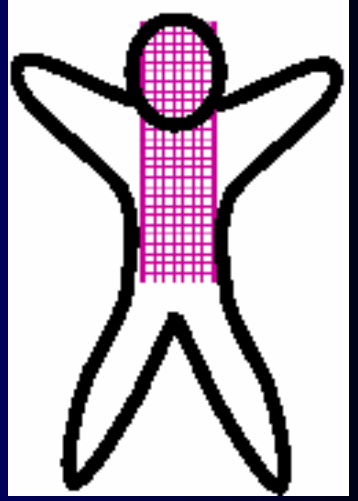


Variola vs. Varicella



	Variola	Varicella
Incubation	10-14 days	14-21 days
Prodrome	Severe	Minimal
Distribution	Centrifugal, Convex	Centripetal, Concave
Evolution	Synchronous	Asynchronous
Crust forms	10-14 days	4-7 days
Crust detaches	14-28 days	<14 days
Infective until	Eschars detach	Lesions crust

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Molluscum contagiosum

Hand, foot, and mouth disease (Coxsackievirus)

Scott Norton, MD

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Disseminated HSV

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Herpes Zoster

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Pustular Drug Eruption

Scabies

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Monkeypox

- 1958 – found in lab monkeys
- 1970 - human disease
- June 2003 – first US cases
- Reservoir – animals (prairie dogs)
- Transmission – aerosol / direct contact
- Less infectious and lethal than smallpox

www.mcw.edu/derm

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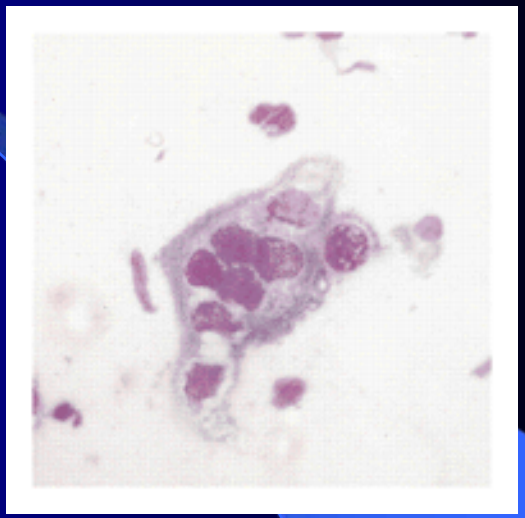
Smallpox
Complications

- Sepsis/toxemia
  - Circulating immune complexes
  - Usual cause of death
- Encephalitis
- Blindness
- Secondary bacterial infection - uncommon

Smallpox

- Immediate ID or Derm consult
  - Activate infection control measures
- Lab testing for DDx
  - Electron microscopy, culture
  - DFA (direct fluorescent antibody test)
  - Polymerase chain reaction
  - Tzanck smear
    - confirms varicella and herpes simplex and zoster
- Report to state health department immediately!!!!



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Evaluating Patients for Smallpox: Acute, Generalized Vesicular or Pustular Rash Illness Protocol

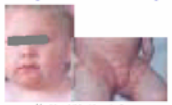
Clinical case definition of smallpox: an illness with acute onset of fever ≥101°F followed by a rash characterized by firm, deep-seated vesicles or pustules in the same stage of development without other apparent cause.

There have been no naturally occurring cases of smallpox anywhere in the world since 1977.

A suspected case of smallpox is a public health and medical emergency.

Report ALL *suspected* cases immediately (without waiting for lab results) to:
1. Hospital Infection Control ( ) _____ or ( ) _____
2. _____ health department ( ) _____ or ( ) _____
3. _____ health department ( ) _____ or ( ) _____

Images of Chickenpox (Varicella)


Healthy child with varicella—note centripetal distribution of rash


Day 3


Lesions are in different stages of development


Pregnant woman with varicella


Healthy adults with varicella


Bacterial superinfection of varicella lesions

Images of Smallpox

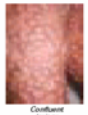

Day 3

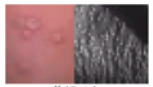

Day 5


Day 7

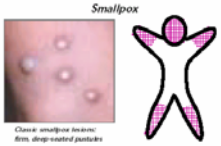

Most patients with smallpox have lesions on the palms or soles


All lesions are in same stage of development


Confluent lesions


Umbilicated lesions


Chickenpox (varicella)
Isolomic superficial vesicles


Smallpox
Classic smallpox lesions: firm, deep-seated pustules

Risk of Smallpox

High Risk of Smallpox → Report Immediately
1. Febrile prodrome (defined below) AND
2. Classic smallpox lesions (defined below and photo at right) AND
3. Lesions in same stage of development (defined below)

Moderate Risk of Smallpox → Urgent Evaluation
1. Febrile prodrome (defined below) AND
2. One *other* MAJOR smallpox criterion (defined below)

OR

1. Febrile prodrome (defined below) AND
2. ≥4 MINOR smallpox criteria (defined below)

Low Risk of Smallpox → Manage as Clinically Indicated
1. No febrile prodrome OR
2. Febrile prodrome and <4 MINOR smallpox criteria (defined below)

MAJOR Smallpox Criteria

•**FEBRILE PRODROME**: occurring 1-4 days before rash onset: fever ≥101°F **and** at least one of the following: prostration, headache, backache, chills, vomiting or severe abdominal pain. The fever may drop with rash onset.

•**CLASSIC SMALLPOX LESIONS**: deep-seated, firm/hard, round well-circumscribed vesicles or pustules; may be umbilicated or confluent

•**LESIONS IN SAME STAGE OF DEVELOPMENT**: on any one part of the body (e.g., the face, or arm) all the lesions are in the same stage of development (i.e. all are vesicles, or all are pustules)

MINOR Smallpox Criteria

•Centrifugal distribution: greatest concentration of lesions on face and distal extremities

•First lesions on the oral mucosa/palate, face, forearms

•Patient appears toxic or moribund

•Slow evolution: lesions evolve from macules to papules→pustules over days (each stage lasts 1-2 days)

•Lesions on the palms and soles

Differentiating Varicella from Smallpox

Varicella is a common condition that is most likely to be confused with smallpox. How varicella (chickenpox) differs from smallpox:

•No or mild prodrome

•Lesions are superficial vesicles: "dewdrop on a rose petal" (see photo, above right)

•Lesions appear in crops; on any one part of the body there are lesions in different stages (papules, vesicles, crusts)

•Centripetal distribution: greatest concentration of lesions on the trunk, fewest lesions on distal extremities. May involve the face/scalp. Occasionally entire body equally affected.

•First lesions appear on the face or trunk

•Patients rarely toxic or moribund

•Rapid evolution: lesions evolve from macules → papules→ vesicles →crusts quickly (<24 hours)

•Palms and soles rarely involved

•Patient lacks reliable history of varicella or varicella vaccination

•50-80% recall an exposure to chickenpox or shingles 10-21 days before rash onset

Common Conditions That Might be Confused with Smallpox

Condition	Clinical Clues
Varicella (primary infection with varicella-zoster virus)	Most common in children <10 years; children usually do not have a viral prodrome
Disseminated herpes zoster	Immunocompromised or elderly persons; rash looks like varicella, usually begins in dermatomal distribution
Impetigo (*Streptococcus pyogenes, Staphylococcus aureus*)	Honey-colored crusted plaques with bullae are classic but may begin as vesicles; regional not disseminated; patients generally not ill
Drug eruptions and contact dermatitis	Exposure to medications; contact with possible allergens
Erythema multiforme minor	Targetoid lesions on hands and feet (including palms and soles)
Erythema multiforme (incl. Stevens Johnson Syndrome)	Major form involves mucous membranes and conjunctivae
Enteroviruses incl. Hand, Foot and Mouth disease	Summer and fall; fever and mild pharyngitis at same time as rash; distribution of small vesicles on hands, feet and mouth or disseminated
Disseminated herpes simplex	Lesions indistinguishable from varicella; immunocompromised host
Scabies; insect bites (incl. fleas)	Pruritis; in scabies, look for burrows (vesicles and nodules also occur); flea bites–patient usually unaware of flea exposure; patient not ill
Molluscum contagiosum	May disseminate in immunosuppressed persons

Photo credits: Dr. Thomas Mack, Dr. Barbara Watson, Dr. Scott A. Norton, Dr. Patrick Alguire, Dr. Karin Gabl, DERMIS, World Health Organization

Department of Health and Human Services
Centers for Disease Control and Prevention

For questions about this protocol or inquiries about smallpox you may call the Centers for Disease Control and Prevention: Days (404) 639-3532; nights/weekends/holidays: (770) 488-7100

Smallpox
Management of Patients

- Supportive
- Isolation
- “Ring” vaccination (effective if given within 3-4 days of exposure)

VACCINATION

- 'Vaccus' – cow
- Jenner 1796 using material from cowpox lesions
- Vaccinia – a live virus vaccine

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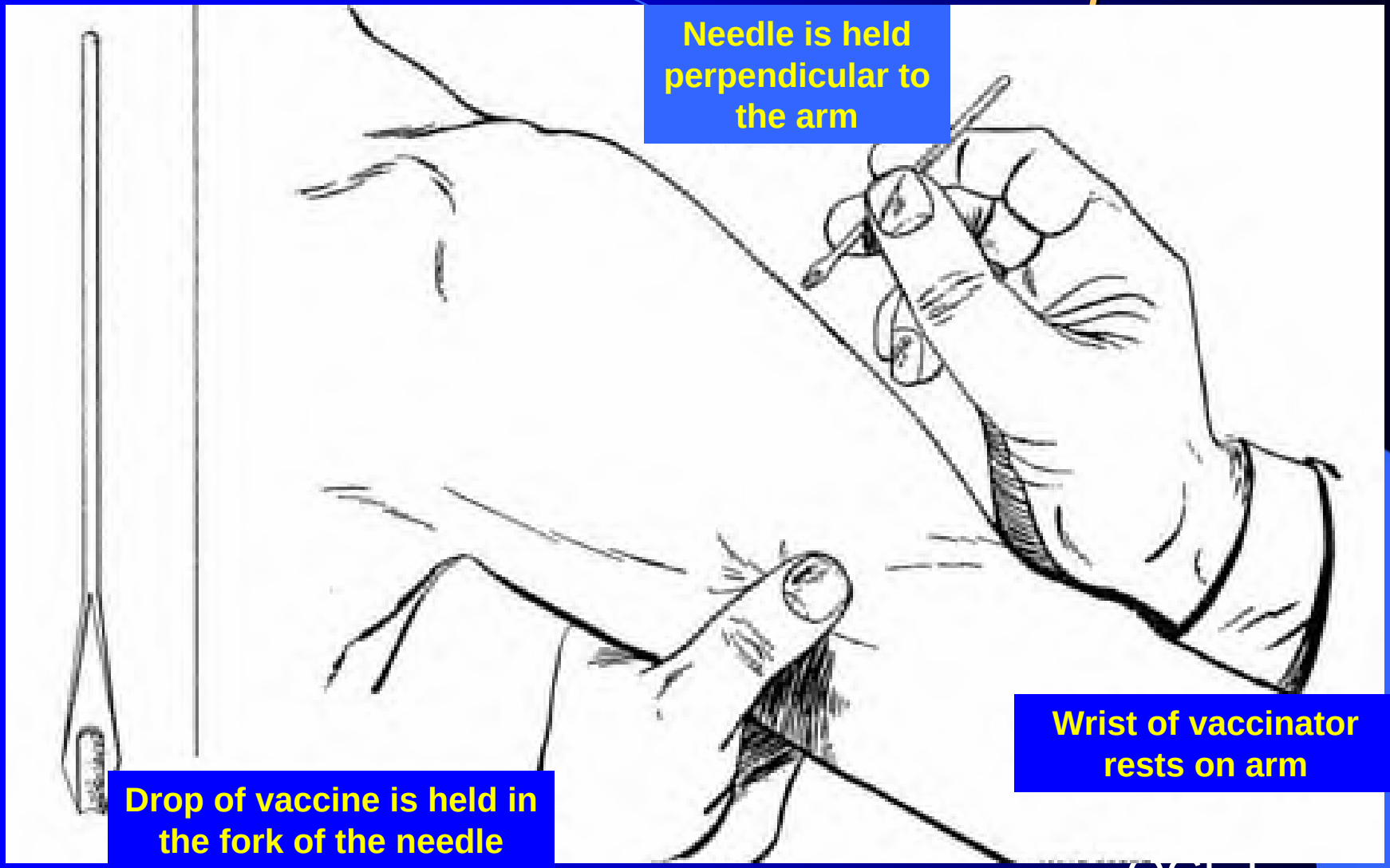
Multipuncture Vaccination with Bifurcated Needle – Scarification Technique



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Smallpox Vaccination

Contraindications for non-emergency *vaccine use*

- Immunodeficiency states or immunomodulating meds
- Life-threatening allergic reactions
- Pregnancy
- Cardiovascular diseases
- Skin diseases
  - Atopics or epidermal disrupting diseases
  - Household members with these

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Smallpox Vaccination
Localized Skin Reactions

- Robust primary
- Autoinoculation
- Peri-ocular

Robust Primary Reaction

Clayton Wheeler, MD

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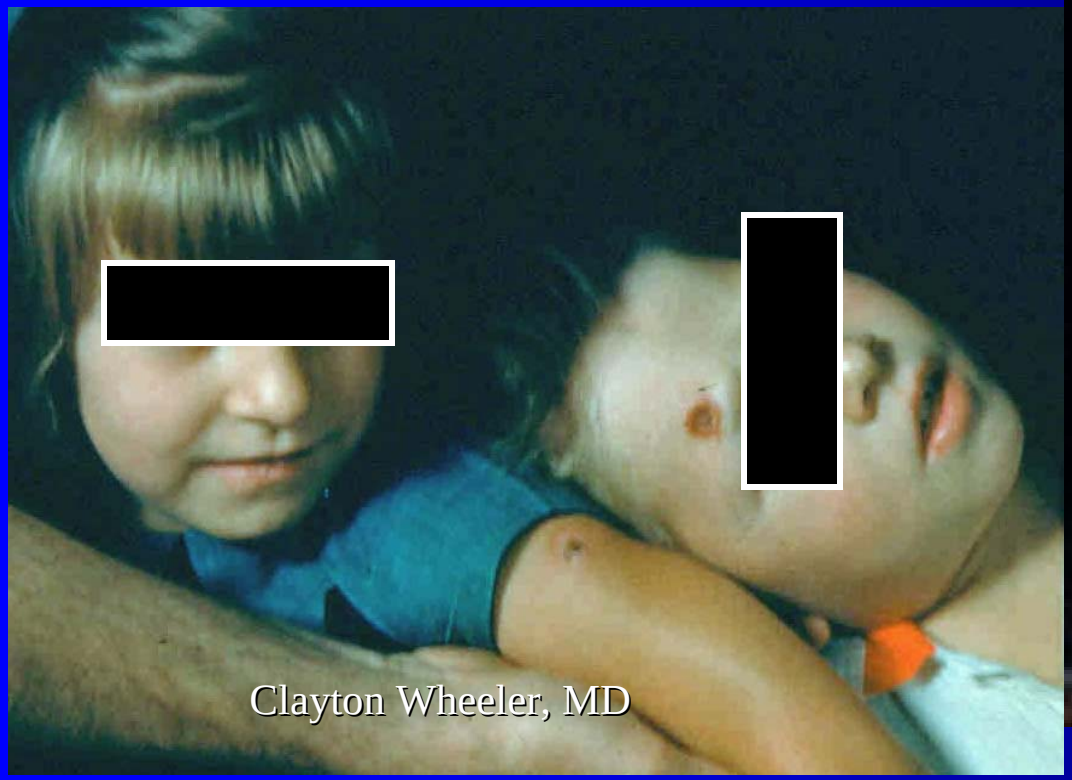
Accidental Vaccinia (Autoinoculation)



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Periocular Vaccinia

Smallpox Vaccination *Generalized Skin Reactions with Systemic Symptoms*

- Generalized vaccinia – distant site viremic spread
- Progressive vaccinia – progressive necrosis
  - Vaccinia necrosum / Vaccinia gangrenosum
- Erythema multiforme major (Stevens-Johnson Syndrome)
  - Mucocutanous reaction to antigenic stimuli
- Eczema vaccinatum – localized or systemic dissemination in eczema/atopics (& history of)

Generalized Vaccinia

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Progressive vaccinia (vaccinia necrosum, vaccinia gangrenosum)

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Erythema multiforme major (Stevens Johnson)

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Eczema vaccinatum

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Eczema Vaccinatum

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Household Transmission of Vaccinia Virus form Contact with a Military Smallpox Vaccinee

- First reported EV case since 1988
- Active-duty father vaccinated on 1/26/07
- History of childhood eczema and 2 of 3 children with eczema
- Deployment delayed and unplanned visit with family 2/16-20
- Reported that vaccination site had scabbed over, scab had separated, and was kept covered (not confirmed)
- 3/3/07, 28 month old boy with severe eczema/failure to thrive presents with generalized papular and vesicular rash on face/neck, UE
- History of fever since 3/1, skin lesions since 2/24
- 3/7/07 umbilicated lesions on 50% of skin surface

MMWR May 18, 2007; 56(19); 478-481

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Household Transmission of Vaccinia Virus form Contact with a Military Smallpox Vaccinee

- 3/8/07 – PCR positive for orthopox DNA, supporting diagnosis of eczema vaccinatum (EV)
- 3/8 – 3/28 treated with Vaccinia Immune Globulin Intravenous (VIG) and cidofovir, vasopressor support, mechanical ventilation
- Investigation anti-viral ST-246 (Emergency IND use), a smallpox drug candidate with antiorthopoxvirus activity inhibiting virus maturation
- 4/19 – discharged after 48 days of hospitalization

MMWR May 18, 2007; 56(19); 478-481

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Household Transmission of Vaccinia Virus form Contact with a Military Smallpox Vaccinee

- 3/6 Mother with mild vesicular lesions on face (rested on child's abdomen in hospital) PCR positive ; 3/10 treated with VIGIV and lesions scabbed over within 72 hours
- 23 family contacts and 73 health care workers monitored daily for 21 days – no other cases
- 3/13 environmental swabbing at home positive PCR
- Cell culture from booster seat, toy, slipper contained viable virus
- 3/23 – disinfection procedures (steam cleaning, phenolics)

MMWR May 18, 2007; 56(19); 478-481

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FIGURE. Abdomen and chest of a boy aged 28 months with a rash of umbilicated lesions caused by eczema vaccinatum — United States, 2007

Photo/John Marcinak

Smallpox Vaccination
*Primary Complication Rates**

*Rate per million vaccinees - all ages

Erythema multiforme	266
Accidental inoculation	242
Post-vaccinial encephalitis	165
Generalized vaccinia	39
Progressive vaccinia	12
Eczema vaccinatum	2

Lane et al. *J Infect Dis.* 122(4):307. 1970.

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DoD Smallpox Vaccination Dec 13, 2002 – May 28, 2003

- 450,293 vaccinated
- Dermatological complications
  - 38 autoinoculation (non-ocular)
  - 36 mild generalized vaccinia
  - 21 vaccinia transfer to contacts
  - 10 ocular auto inoculation
  - 6 cases cellulitis
  - 1 erythema multiforme
  - No eczema vaccinatum
  - No progressive vaccinia

JAMA 2003;289:3278-3282

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DoD Smallpox Vaccination

- Neurological
  - 1 documented encephalitis
  - 23 other neurologic events with unclear association to the vaccine
- Cardiac
  - 37 acute myopericarditis: primary / males
  - 8 other cardiac events 2-12 days after

- *JAMA 2003;289:3278-3282*

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Reported Adverse Events

- Jan 24-Dec 31, 2003; 39,213 civilians vaccinated
  - Eczema vaccinatum: none
  - Generalized vaccinia: 2-suspected, 1-confirmed
  - Inadvertent inoculation (nonocular):
    11-suspected and 9-confirmed
  - Ocular vaccinia: 1-suspected, 2 confirmed
  - Stevens Johnson: none
  - Myo/percarditis: 16-suspected, 5-probable, 0-confirmed
  - Encephalitis: 1-suspected

MMWR 53(05); 106-107

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Your Role in BT as a Health Care Professional

- Education
  - www.bt.cdc.gov
- Be aware
- Be involved

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What Can You Do? Volunteer

- Medical Reserve Corps
  - www.medicalreservecorps.gov
- National Disaster Medical System (NDMS)
  - Disaster Medical Assistance Teams (DMAT)
  - www.ndms.dhhs.gov

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The US Public Health Service (USPHS)

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USPHS Mission

- Protecting, promoting, and advancing the health and safety of the Nation
  - Rapid and effective response to public health needs
  - Leadership and excellence in public health practices
  - The advancement of public health science

USPHS and Federal Agencies

- Agency for Healthcare Research and Quality (AHRQ)
- CDC / ATSDR
- CMS
- FDA
- HRSA
- IHS
- NIH
- SAMHSA
- Office of Secretary HHS
- Program Support Center
- CIA
- DHS/USCG
- DoD
- Justice/BoP/US Marshals Service
- EPA
- Interior/NPS
- USDA

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USPHS Force Strength
5983 Officers

- 1314 nurses
- 1097 physicians
- 923 pharmacists
- 857 health services officers
- 460 dentists
- 398 engineers
- 377 environmental health officers
- 254 scientists
- 120 therapists
- 94 dieticians
- 89 veterinarians

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Disaster Response -- Tsunami

- Medical and mental health care (USNS Mercy and in the field)
- Environmental health
- Disease control and surveillance

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Disaster Response -- Katrina

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Review

- Overview of bioterrorism (BT)
- Review and update on BT agents with skin manifestations
  - Emphasis on anthrax and smallpox
- Your role in preparedness and response

boris.lushniak@fda.hhs.gov

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