

## Smallpox



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- Orthopox Viruses (DNA):
  - Monkeypox, Gerbilpox, Camelplex, others
  - Cowpox
  - Vaccinia
  - Variola
- Diseases:
  - Variola Major: mortality 30+%
  - Variola Minor: mortality  $\leq$  1%

## Smallpox

- 1796 Edward Jenner demonstrated that cowpox protected against Smallpox.
- 1949 Last case Smallpox in US
- 1967 WHO begins global campaign to eradicate disease
- 1972 Routine smallpox vaccination ceased US (age 1)
- 1977 Eradication of smallpox. Last case of Variola Minor in Somalia.
- 1980 World Health Assembly recommend all countries cease smallpox vaccination. WHO recommends all labs destroy samples of virus or send to:
  - Institute of Virus Preparations, Moscow
  - CDC in Atlanta

## Smallpox

- 1990: US unveils plans to sequence smallpox DNA, destroy remaining Russian and American stores of disease by 1993
- 1998: Extent of Soviet weapons program becomes public when USSR bioweapons chief Ken Alibek defects.
- 1998: Clinton postpones destruction of last smallpox
- 2002: Three phase smallpox vaccination program proposed
  - Phase One: Smallpox response teams
  - Phase Two: HCWs
  - Phase Three: Public

## Smallpox

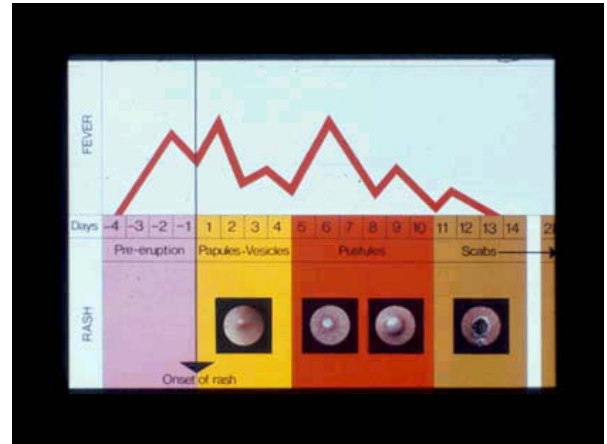
- Disease most prominent in winter and early spring (possibly because virus survives poorly with increased temperature and humidity.)
- Incubation:
  - 12-14 days with range 7-17 days
- Transmission:
  - Person-person by droplets or aerosols; or direct contact with contaminated clothing/bedding. (within 6 feet most common)
  - Infectious with onset rash. Not during prodrome. Until last scab separated.
  - Risk to household contact and those with face to face contact
  - Less contagious than measles, influenza. More contagious than TB. 36-88% unvaccinated household contacts become infected.

## Smallpox

- Symptoms:
  - Prodrome: high fever, malaise, prostration, headache, backache (non-specific) lasting 3-4 days
  - Maculopapular rash, starting on oral mucosa and pharynx
  - Over 1-2 days rash becomes papular then vesicular then pustular
    - Rash is everywhere in same stage.
    - Prominent on hands, soles, extremities, face
    - Fever decreases after rash appears (Biphasic fever curve)
  - Crusts over 8-9 days leaving pitted scarring.
  - Death usually in 2<sup>nd</sup> week from toxemia, circulating immune complexes and soluble Variola antigens

## Smallpox

- Presentations:
  - **Ordinary**
    - Discrete
    - Semi-confluent
    - Confluent
  - **Flat** – 20% of cases. Severe.
  - **Hemorrhagic** – 18% of cases. Intense erythema and hemorrhages. Often misdiagnosed as meningococemia or drug eruption. Very lethal.
  - **Modified Smallpox**: Milder symptoms. 25% of individuals with history of vaccination. (Unlikely in US now since vaccination stopped over 30 years ago). Lesions evolve more rapidly.



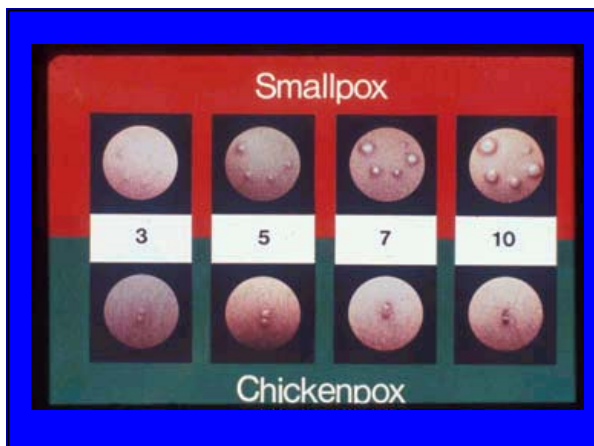
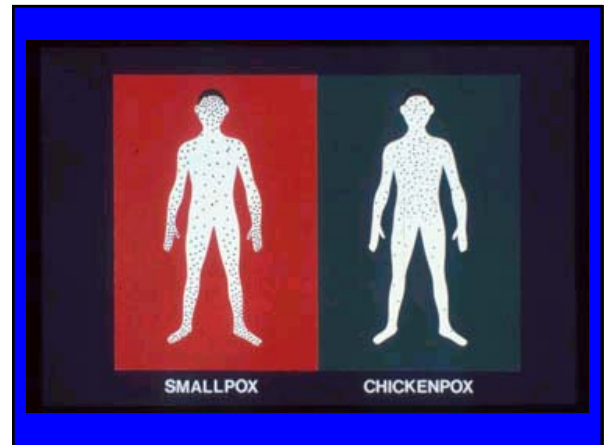


### Smallpox

- **Diagnostic tests:**
  - Not a lot of modern data about lab tests
  - Specimens should be collected by someone who has been vaccinated and who wears gloves/mask
  - Send vesicle fluid to Public Health authorities in double sealed container. Laboratory examination requires high-containment facilities
    - EM examination – orthopox virus (brick shaped virions)
    - PCR techniques, DNA probes.
    - Definitive ID: cell culture or culture on chorioallantoic egg membrane and characterization of strains by use of various biologic assays (PCR, restriction fragment length polymorphisms)
- **Treatment:**
  - Supportive.
  - Experimental - cidofovir

### Differentiating Smallpox - Chickenpox

	SMALLPOX	CHICKENPOX
<b>FEVER</b>	2 to 4 days before rash	At time of rash
<b>RASH</b>		
• <b>Appearance</b>	Pocks in same stage	Pocks in several stages
• <b>Development</b>	Slow	Rapid
• <b>Distribution</b>	More pocks on arms and legs	More pocks on body
• <b>On palms and soles</b>	Usually present	Usually absent
<b>DEATH</b>	Usually 1 in 10 die	Very uncommon





### Smallpox Vaccination

- Vaccinia
  - >95% protection against disease
  - Duration of immunity never satisfactorily measured.
    - antibody levels decrease after 5-10 years
    - levels may persist 30 years following second/third vaccination
  - Two types – live virus: multiplies in superficial layers of skin.
    - DryVax: calf-lymph vaccine (Wyeth, Aventis) – produced by infection of the skin of calves. Contains antibiotics and preservatives.
    - Tissue culture cell vaccine (Baxter)
  - Vaccination effective if given within 4 days post-exposure
  - Must document “Take”

### Contraindications to Smallpox Vaccine

- Immunodeficiency (HIV, organ transplant, malignancy, autoimmune diseases, immunosuppressing medications)
- Atopic dermatitis or eczema (or home contact with these conditions)
- Other skin conditions: burns, impetigo, psoriasis etc.
- Pregnancy now or possible within the next month (home contact with pregnant individual).
- History anaphylactic reaction to: polymixin B, streptomycin, tetracycline, neomycin, phenol.
- Moderate or severe acute illness
- Not recommended for persons less than age 18
- If actual exposure to Smallpox disease, the conditions/factors listed above are no longer contraindications



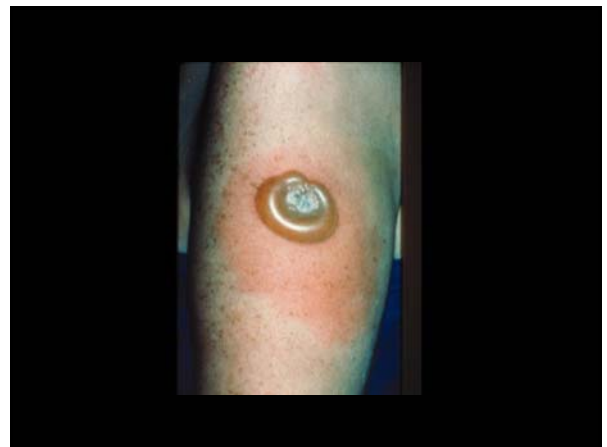


Normal reactions to Vaccinia vaccination

Lymphadenopathy	25-50%
Myalgia, headache, chills, nausea, fatigue	0.3-37%
Fever > 37.7degrees	2-16%



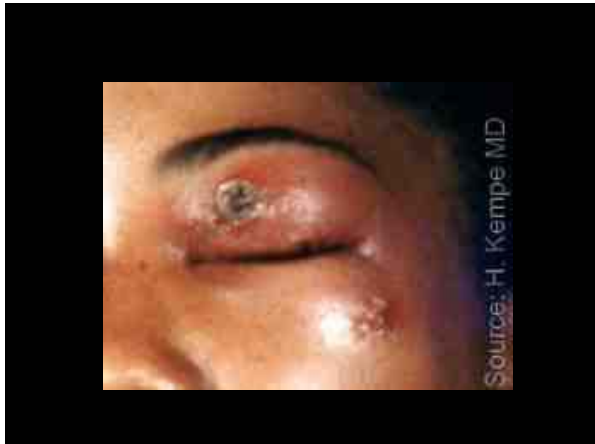






- ### Adverse Reactions to Smallpox Vaccination (Vaccinia)
- Autoimmune injury
  - Accidental Implantation (including cornea)
  - Bacterial infection
  - Generalized vaccinia
  - Post-vaccinial encephalitis

- ### Accidental Implantation
- The vaccination site contains high titers of vaccinia virus
  - Any disrupted skin can lead to implantation, but the severity of accidental implantation parallels the degree of skin involvement
  - Covering the lesion and screening of vaccinees minimizes the risk.
  - HCWs may continue to work and care for immunosuppressed patients.





### Accidental Implantation

- Treatment:
  - One or few lesions: none
  - Multiple or confluent lesions over large portions of the body: Vaccinia Immune globulin (VIG) 0.6 mg/kg IM
  - (Vaccinia Immune Globulin is contraindicated for vaccinia keratitis)

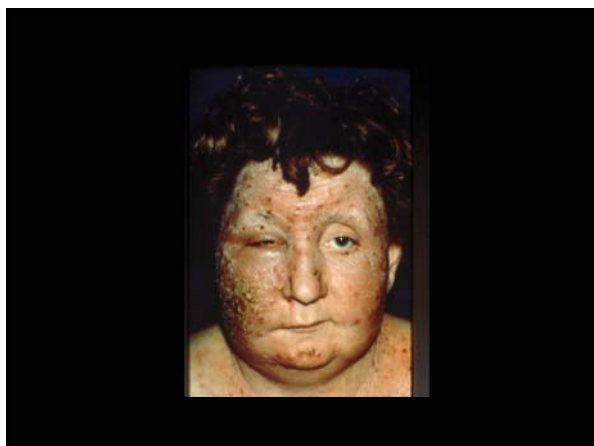
### Generalized Vaccinia

- The result of systemic spread of virus from vaccination site.
- It is a totally benign complication of primary vaccination
- Rare



### Generalized Vaccinia

- Usually no treatment required. If extensive lesions, use antiglobulin.





### Progressive Vaccinia

- Implies T cell deficiency:
  - Of 900,000 HIV infected in US – 300,000 don't know it, Cancer patients, Organ transplant patients
- The most severe complication of vaccination
- Life threatening
- Also called:
  - vaccinia necrosum
  - vaccinia gangrenosa
  - disseminated vaccinia



### Progressive Vaccinia

- Treatment: massive doses of VIG
- Antiviral therapy: cidofovir shows effect in vitro (animal studies pending)

### Eczema Vaccinatum

- Individuals with eczema (atopic dermatitis) are at special risk from implantation of vaccinia into the diseased skin, sometimes with a fatal outcome. Condition results from implantation and subsequent spread.
- Atopic dermatitis implies both a skin abnormality (disrupted skin) and an immunologic difference (underlying T-cell immunologic defect)
- If smallpox is not an immediate risk, vaccination should not be performed in these patients and they should not be in contact with vaccinees.



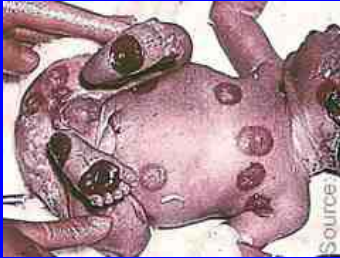
**Eczema vaccinatum**

- Requires urgent treatment with VIG
- IM-VIG at 0.6-1.0 ml/kg body weight. If extensive, 5-10 ml/kg IM-VIG may be given, divided into multiple doses and given over several days.
- With early recognition and appropriate use of vaccinia immune globulin (VIG) mortality can be reduced to zero.
- If VIG treatment is delayed viremia ensues with spread of infection.



### Congenital Vaccinia

- Rare
- Usually due to third trimester vaccination.



### Smallpox Vaccine Adverse Effects – first dose

- Postvaccinial encephalitis 1 / 115,000 – 415,000
- Progressive vaccinia 1 / 590,000 – 1,000,000
- Eczema vaccinatum 1 / 94,000 -- 220,000
- Generalized vaccinia 1 / 4,500 – 57,000
- Inadvertent inoculation 1 / 1,900 – 37,000

**Table 1.** Complications of Smallpox Vaccination in the United States for 1968—Centers for Disease Control and Prevention National Survey<sup>1,2</sup>

Vaccination Status, Age, y	Estimated No. of Vaccinations	No. of Cases						Total
		Postvaccinial Encephalitis <sup>a</sup>	Progressive Vaccinia <sup>a</sup>	Eczema Vaccinatum <sup>a</sup>	Generalized Vaccinia	Accidental Infection	Other	
Primary vaccination†	5,594,000	16 (4)	5 (2)	58	131	142	66	418
Revaccination	8,574,000	0	6 (2)	8	10	7	9	40
Contacts	1	0	0	60 (1)	2	44	8	114
<b>Total</b>	<b>14,168,000</b>	<b>16 (4)</b>	<b>11 (4)</b>	<b>126 (1)</b>	<b>143</b>	<b>193</b>	<b>83</b>	<b>572</b>

<sup>a</sup> Data in parentheses indicate number of deaths attributable to vaccination.

<sup>b</sup> Data include 11 patients with unknown vaccination status.

<sup>c</sup> Based on 1968 contacts survey not vaccination.

### Response to Smallpox Exposure

- Isolate
- Vaccinate all household contacts and those with face to face exposure (no contraindications – Smallpox worse than any Vaccinia complication)
- Vaccinate within 3 days – may prevent disease. Within 4 days may significantly ameliorate subsequent illness.
- Contacts take temperature daily – Isolate if temp > 38 during 17 days post exposure
- Hospital: Negative pressure isolation. Autoclave/incinerate laundry
- Preferred: Manage out of hospital

### Hospital transmission

- **1950-1971:** 49 imported outbreaks in Europe
  - 50% cases in medical setting
  - Most transmission – contact within 6 feet.
- **Decontamination:**
  - If released as an aerosol. May persist for as long as 24 hours under favorable conditions.
  - Vaccinia in scabs is more durable – may survive for a few weeks (3-12) but is less transmissible.

### Bioterrorism

- **French-Indian Wars 1754-1767.** British soldiers distributed blankets that had been used by smallpox patients to Indians. Epidemics ensued killing >50% of many affected tribes.
- **Why:**
  - High case fatality rate
  - Person – person spread
  - Lack of population immunity
  - Lack of treatment
- **Europe 1960s-1970s:** Imported Smallpox in Dec-April months resulted in high transmission, 10-20 second generation cases from single patient with widespread concern/panic.
- **1980: Soviet Union** began program to mass produce smallpox as bioweapon (aerosol release) and adapt for use in bombs, missiles (Ken Alibek former deputy director of Soviet civilian bioweapons program)

**Table 2. Expected Deaths Due to Smallpox and Vaccination, According to the Attack Scenario and Control Strategy.**

Control Strategy and Cause of Death*	Hoax	Laboratory Release	Human Vectors	Building Attack	Airport Attack	
					Low Impact	High Impact
					<i>number of deaths</i>	
Contact vaccination and isolation alone	0	7	19	300	2735	54,728
Smallpox	0	7	19	300	2733	54,691
Vaccination	0	0	0	0	2	37
Post-attack vaccination of health care workers	0	7	19	299	2757	54,698
Smallpox	0	7	18	298	2751	54,643
Vaccination	0	0	1	1	26	55
Post-attack vaccination of health care workers and public	0	13	26	296	3113	53,037
Smallpox	0	6	18	286	2633	52,541
Vaccination	0	7	8	10	482	496
Prior vaccination of health care workers	25	28	37	213	2218	43,901
Smallpox	0	3	12	188	2192	43,852
Vaccination	25	25	25	25	26	49
Prior vaccination of health care workers and post-attack vaccination of public	25	34	44	215	2596	42,813
Smallpox	0	3	11	181	2114	42,320
Vaccination	25	31	33	34	482	493
Prior vaccination of health care workers and public	482	484	484	535	1123	13,142
Smallpox	0	2	2	53	641	12,857
Vaccination	482	482	482	482	482	485

\* Contact vaccination and isolation are part of all control strategies.

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