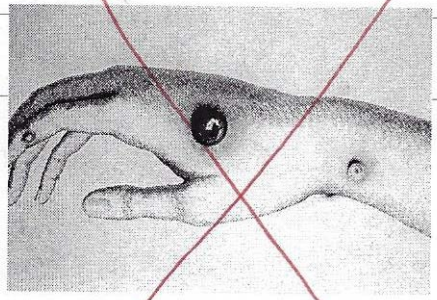
Smallpox Vaccination Strategy

D. A. Henderson, MD, MPH
Department of Health and Human Services
Johns Hopkins University

"On May 8, 1980, WHO announced that smallpox had been eradicated from the planet... Soon after the WHO announcement, smallpox was included in a list of viral and bacterial weapons targeted for improvement in the 1981-85 Five-Year Plan.... Where other governments saw a medical victory, the Kremlin perceived a military opportunity...the Soviet military command issued an order to maintain an annual stockpile of 20 tons."

Alibek, 1998

Edward Jenner

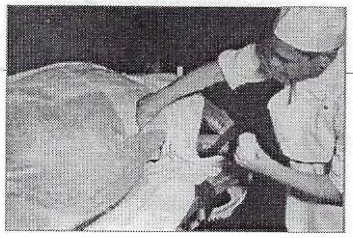


Cowpox on the hand of Sarah Nelmes

Smallpox vaccine--landmarks

- 1798 –Cowpox, the first vaccine
- Until late 1800s – arm-to-arm spread
- Late 1800s to 1980 – Usually grown on calves, sheep, water buffalo
  - Two principal strains
    - New York City Board of Health
    - Lister Institute strain

Scarifier developed by Wyeth



Vaccine collection from cows seeded with vaccinia

DHHS Office of the Secretary

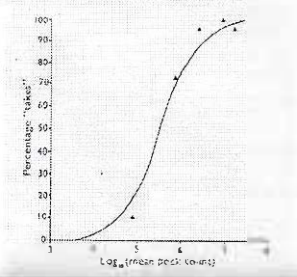
Smallpox Vaccines – International Standards

	1959	1965
Titer – pfu/ml	5×10^7	1×10^8
Bacterial count/ml (non-pathogens)	<1000	<500

Seed lot system

DHHS Office of the Secretary

Vaccine Titer and Primary Takes



Cockburn, 1959

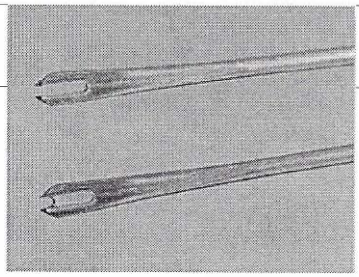
DHHS Office of the Secretary

Vaccine Production Laboratories - 1968

	No.	Strains of Vaccinia* Lister	NYCBOH	Other
Americas	9	2	5	2
Europe	27	8	0	19
Africa	9	3	0	6
Asia/Oceania	19	7	0	12
	64	20**	5	39

*For production – all grown on calves, sheep, or water buffalo
**By 1971 the number was 39

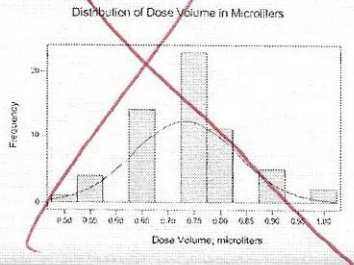
DHHS Office of the Secretary



Bifurcated Needles

DHHS Office of the Secretary

Bifurcated Needle Dose Volume – 15 vs. 3



DHHS Office of the Secretary

U.S. Smallpox Vaccines

	No. of doses
▪ Wyeth DryVax	15 million
▪ Manufactured 1978-9	
▪ Aventis Pasteur	85 million
▪ Manufactured ca. 1958	
▪ Acambis /Baxter	209 million
▪ Manufactured 2002	

DHHS Office of the Secretary

Wyeth DryVax 15 million

- NYCBH strain, calf skin, lyophilized
- Licensed product
- Efficacy (take rate) in unvaccinated adults*
  - Undiluted 97% (103/106)
  - 1:5 99% (232/234)
  - 1:10 97% (335/340)
- Stability after rehydration 30 days at 2-8°C

*NEJM 346: 1265-1274, 2002

DHHS Office of the Secretary

Aventis Pasteur -"Wetvax" 85 million

- NYCBH, calf skin, wet frozen, glycerol
- Emergency use only -- IND status
- 100 dose vials: can be diluted 5:1

DHHS Office of the Secretary

ACAM 1000/2000 209 million

- Acambis and Acambis/Baxter
- NYCBH strain -- Grown in Vero cells
- Lyophilized, 100 dose vials
- In Phase II trials
- Licensure -- early 2004

DHHS Office of the Secretary

Intravenous Vaccine Immune Globulin --IVIG

- Cangene, a Canadian manufacturer
  - Plasma from paid revaccinated donors
- Sufficient now to treat serious reactions among 32 million vaccinees
- By June, sufficient to deal with 300 million vaccinees

DHHS Office of the Secretary

MVA – A Next Generation Vaccine?

- Non-replicating attenuated vaccinia strain (Modified Vaccinia Ankara)
- Vaccination by IM –either 2 doses or 1 dose followed by Dryvax
- Contract awarded for development and initial manufacturing of MVA
- Initial phase I trials have begun

DHHS Office of the Secretary

Lc16m8 – A Next Generation Vaccine?

- A temperature-sensitive clone of the Lister strain developed in Japan in the 1970s
- Trials to begin soon in US and Japan
- Grown in primary rabbit kidney
- Tested in 50,000 Japanese children – less skin reaction and fewer systemic symptoms; apparently similar serological responses to Lister strain

DHHS Office of the Secretary

Options for Vaccination Before an Event

- **Vaccinate no one**
- **Vaccinate those at highest risk, candidates:**
  - **Healthcare workers**
  - **First responders**
  - **Postal workers**
  - **Other essential persomel**
- **Vaccinate anyone desiring to be vaccinated**
  - **Recommend vaccination**
  - **Recommend against vaccination**
- **Make vaccination compulsory**

DHHS Office of the Secretary

Smallpox Vaccine Expected Adverse Events

- **Life-threatening complications No/million**
  - **Post-vaccination encephalitis 2-3**
  - **Progressivevaccinia 1-2**
  - **Eczema vaccinatum 10-15**
- **Less serious**
  - **Rash, fever, accidental inoculation**
- If 100 million vaccinated -- 100-400 deaths and some 1500 to 2000 serious complications perhaps requiring hospitalization.

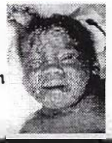
DHHS Office of the Secretary

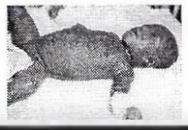
Vaccination Adverse Events

Accidental Inoculation

Progressive Vaccinia

Eczema Vaccinatum





DHHS Office of the Secretary

Vaccinia Complications

- The definitive website
- **www.bt.cdc.gov/training/smallpoxvaccine/reactions**

DHHS Office of the Secretary

A Balance of Risks

- What is the likelihood that smallpox will be used as a weapon?
- What will the frequency of adverse reactions be and how will the public deal with this?

DHHS Office of the Secretary

Options for Vaccination Before an Event

- **Vaccinate no one**
- **Vaccinate those at highest risk, candidates:**
  - **Healthcare workers**
  - **First responders**
  - **Postal workers**
  - **Other essential personnel**
- **Vaccinate anyone desiring to be vaccinated**
  - **Recommend vaccination**
  - **Recommend against vaccination**
- **Make vaccination compulsory**

Clinical Course of Smallnox

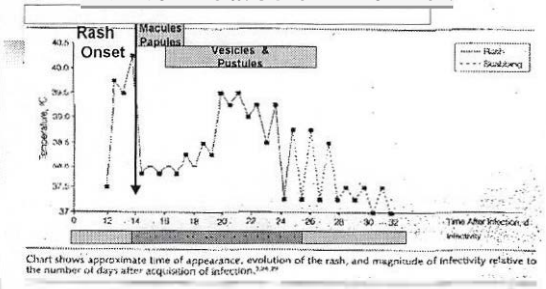


Chart shows approximate time of appearance, evolution of the rash, and magnitude of infectivity relative to the number of days after acquisition of infection.[3,4,7]

JAMA, June 9, 1999—Vol 281, No. 22 2129

Epidemiology of Smallpox
Spread and Virulence

Spread of disease is comparatively slow

- Secondary household attack rates (approx.)

Measles	76%
Chickenpox	74%
Smallpox	58%

- Note slower community spread of smallpox than either measles or chickenpox, both of which can be transmitted before symptoms appear

Epidemiology of Smallpox
Transmission Patterns in Europe: 1958-1973

- Outbreaks: 34
- Cases: 573
  - Due to transmission in hospital: 277 (48%)
  - Due to transmission in home: 143 (25%)
- Hemorrhagic and malignant cases– a threat to hospitals

Bradford, UK (1961)	Hemorrhagic smallpox	10 cases
Germany (1970)	Malignant smallpox	16 cases
Yugoslavia (1972)	Hemorrhagic smallpox	38 cases

- Seasonal variation

Dec to May	24 importations	average=45.6 additional cases
Jun to Nov	10 importations	average=0.5 additional cases

Surveillance

- First persons to detect cases – ER staff
  - Prodromal smallpox illness is usually severe and incapacitating
- Call on 24/7 line to health department
  - Contact of other regional facilities
- Emergency transport of specimens to CDC and LRN network

Containment

- Vaccinate and isolate patient in designated hospital
- Vaccinate all persons who had been in a room with the patient since he became febrile (primary contacts)
- Place primary contacts under surveillance with twice daily temperatures
  - If a primary contact develops fever isolate at home or inspecial facility until diagnosis is known
- Vaccinate all household contacts of primary contacts (secondary contacts)

Other Steps/Principles

- Make vaccine available on request to those in the general geographic area
- Prompt, current, accurate communication to public
- Not generally desirable:
  - Compulsory vaccination
  - Quarantine of city or groups of people
  - Closure of airports, suspension of transport

DHHS Office of the Secretary

Preparatory steps in progress

- Vaccine –
  - Stockpiled--available anywhere in 12 hours
- Each region planning for mass vaccination of population in 5-7 days and to accomodate 500 casualties in negative pressure rooms
- Every ER to have negative pressure rooms for examining all patients with rash and fever
- Educational material to all health care providers and special community education material in local hands

DHHS Office of the Secretary