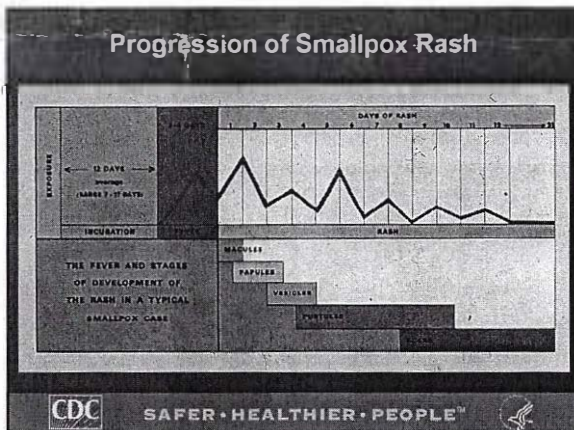
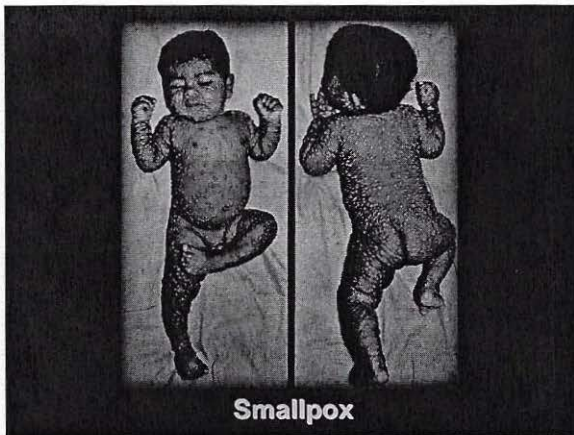
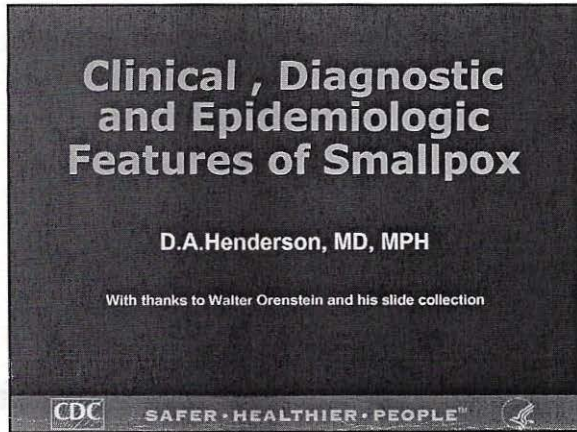


Thanks for the invitation.
Appropriate opportunity to
visit what is one of the
nation's premier med. ctrs.

- I regret that the subject is smallpox
- Last case 25 years ago ¹⁹⁷⁷ - closed a door
 - 81-88 Archival box - good doorstop. - But
 - Given as late as 1993 - confident we had seen the last of "pox."



Most survivors of all diseases known to man -
Virus - no animal reservoir -
to be sustained - continuing chain of transmission

Earliest known cases 3000 years ago - pharaoh.

Problem to mankind throughout history -

20th cent. 200×10^6 deaths. ^{Approx. 1000/generation}

Then, a defect from Soviet Union -

Massive bio weapons prog. (incl. spox).

60000 X 50

Perhaps half of scientists disappeared.
Where the virus might be - impossible to know
Risk of its being used by a terrorist low
but not '0'.

With vaccination stopped 1872 -

large vulnerable population.

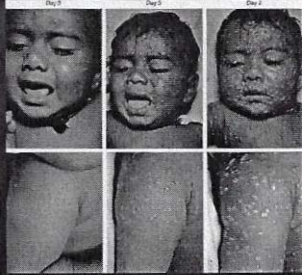
30% death rate - no Rx.

Smallpox with anthrax ^{anthrax} as the two
most serious problems.

Today: Clinical ~~features~~ features of smallpox
followed by a discussion of vaccination.

PROGRESSION OF SMALLPOX

- Incubation Period
- Prodromal illness
- Macules
- Papules-day 3
- Vesicles
- Pustules-day 5
- Scabs
- Scars



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rearmately present by day 3
 Dx ~~definitive~~ definite by day 8

TYPES OF SMALLPOX

- No rash – Variola sine eruptione
- Modified
- Ordinary
- Malignant (flat)
- Hemorrhagic



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Problems
 90%
 few modified
 Malignant
 flat.

ORDINARY SMALLPOX

- Discrete pustules more extensive on face than on trunk



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ORDINARY SMALLPOX

- Pustules are usually present on hands and feet



CDC

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info: palms and soles.

SMALLPOX – FLAT

- Confluent pustules. Skin has texture like crepe rubber. Usually fatal



+ in Fenner F et al. Smallpox and Its Eradication, p33

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HEMORRHAGIC SMALLPOX

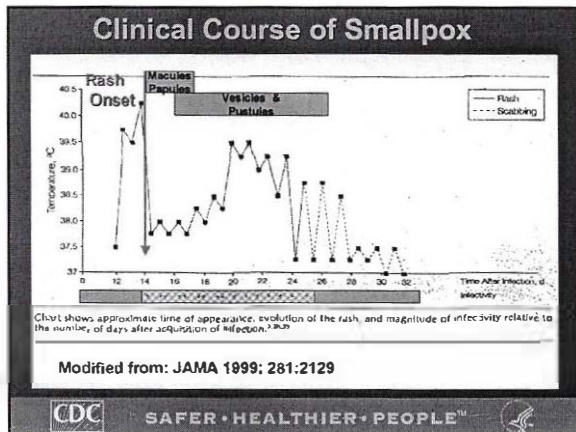


+ in Fenner F et al. Smallpox and Its Eradication, p35

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Stom virus transmission

Smallpox Transmission

- Common: Person – to –person by airborne droplets
 - Face-to-face contact (6-7 feet). No carriers.
- Rare: airborne over long distance
- Rare: as fomites
 - Bedclothes, linens, blankets
- Not transmitted by: food, water

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Bioterrorism:

Aerosol

Not injected terrorists.

Mode of Acquisition of Variola Major from Smallpox Importations in Europe, 1950 – 1971^{*,**}

Mode	Cases	%Total
Hospital Transmission	359	55%
Work-related	51	8%
Family and intimate contacts	129	20%
Casual contacts	63	10%
Miscellaneous	6	1%
Unknown	44	7%

* Excludes 28 importations of unknown or unreported mode of transmission.
 ** J Infectious Diseases 1972; 125: 161-169.

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75%

Types of Persons Who Contracted Smallpox in Hospitals from Smallpox Importations in Europe, 1950 – 1971⁺

Mode	Cases	%Total
Hospital staff and family	146	41%
Hospital clientele	211	59%
– Inpatients	193	91%
– Outpatients and visitors	18	9%

⁺ J Infectious Diseases 1972; 125: 161-169.

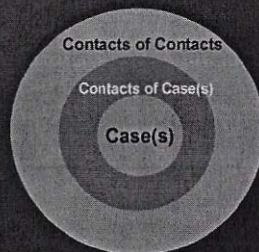


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Search and Containment (Ring Vaccination)

- Search for cases
- Isolate them
- Identify and vaccinate contacts—keep under surveillance
- Vaccinate household members of patient contacts



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Reasons for Success of Ring Vaccination

- Smallpox -easy to diagnose & no carriers
- Almost all transmission is by droplets
- No transmission until after patient becomes sick
- Vaccination protects up to 3 to 4 days after infection



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Summary

- Clinical diagnosis is comparatively straightforward. Few atypical cases
- Laboratory tests are definitive.
- Spread is slower than illnesses such as measles. Similar to rubella, diphtheria and mumps.
- Transmission almost always readily traceable to face-to-face contact.



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Return of Smallpox Vaccination - 2003

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

Turn to guest's presentation -

"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

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Definitive evidence

A reminder

Smallpox prod. facility

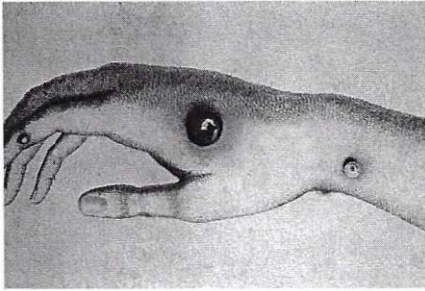
Vaccination - our only weapon



Edward Jenner

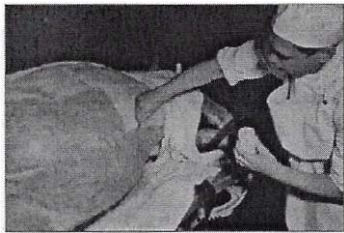
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A bit of history as it's not irrelevant to today.



Cowpox on the hand of Sarah Nelves

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Vaccine collection from
cows seeded with vaccinia

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Scarifier developed by Wyeth

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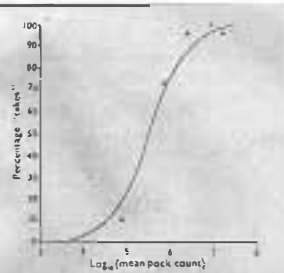
Smallpox Vaccines – International Standards

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

Seed lot system

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Vaccine Titer and Primary Takes



Cockburn, 1959

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1:5

1:10

Vaccine Production Laboratories - 1968

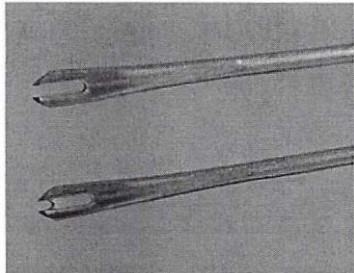
	No.	Strains of Vaccinia*		
		Lister	NYCBOH	Other
Americas	9	2	5	2
Europe	27	8	0	19
Africa	9	3	0	6
Asia/Oceania	19	7	0	12
	64	20**	5	39

*For production – all grown on calves, sheep, or water buffalo

**By 1971 the number was 39

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Two strains



Bifurcated Needles

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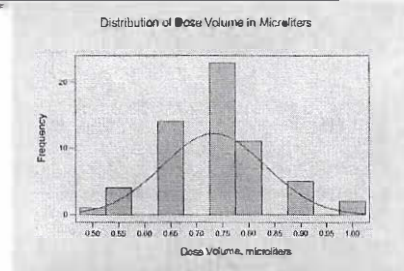
Denon took method

~ 15 strokes in 3 seconds

NOT POKING.

Bifurcated Needle

Dose Volume – 15 vs. 3



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Concern about volume inhaled.

Note replication of virus.

U.S. Smallpox Vaccines

	No. of doses
■ Wyeth DryVax	15 million
■ Manufactured 1978-9	
■ Aventis Pasteur	85 million
■ Manufactured ca. 1958	
■ Acambis ACAM1000	54 million
■ (MRC-5 cell production)	
■ Acambis/Baxter ACAM 2000	155 million
■ Vero cell production	

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Sept 18 - 2000 7 days to 9/11

90 000 doses of vaccine.

Wyeth DryVax

- 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

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Aventis Pasteur - "Wetvax"

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

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1958.

ACAM 1000/ACAM 2000

- Acambis and Acambis/Baxter
- NYCBH strain -- Wyeth seed
- Produced in Vero cells
- Lyophilized, 100 dose vials
- Licensure -- early 2004

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Phase III trials
begin in April

Equislet

Intravenous Vaccine Immune Globulin

- CDC contract with Cangene, Aug. 2002
 - 30,000 treatment units
 - Plasma from paid revaccinated donors
 - Delivery began in Oct. 2002
 - Sufficient now to treat serious reactions among 10 million vaccinees.

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3000 units now. — Complications in
30 x 10⁶

MVA – A Next Generation Vaccine?

- Non-replicating attenuated vaccinia strain (**M**odified **V**accinia **A**nkara)
- Vaccination by IM --either 2 doses or 1 dose followed by Dryvax
- NIH contract awarded for development and initial manufacturing of MVA
- Initial phase I trials have begun
- Purchase contract -- up to 30M doses

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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

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Options for Vaccination Before an Event

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

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Smallpox Vaccine Expected Adverse Events

- Life-threatening complications
 - Post-vaccination encephalitis
 - Progressive vaccinia (vaccinees and contacts)
 - Eczema vaccinatum (vaccinees and contacts)
- Less serious
 - Generalized vaccinia
 - Accidental inoculation
 - Rash and fever
- If 100 million are vaccinated -- 100-400 deaths and some 2000 serious complications perhaps requiring hospitalization.

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Vaccination Adverse Events



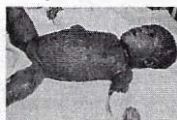
Accidental Inoculation



Progressive Vaccinia



Eczema Vaccinatum



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CONTACT VACCINIA

per million

Conclude a present plan:

~3400 of 5000 hosp.
~450 000 vaccinees
anti-epidemic



Vaccinia Complications

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



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