

Chimellon
 Marver Dr. Raymond.
 S. Pave Heinrich
 Fern (Gru. Johanns.)

Plagues to the West

? Hassan
 o 25 years
 o The book / door stop / out of print -

Smallpox Vaccination Strategy: Lessons from History

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 Latta Lecture
 Omaha, Nebraska
 27 February 2003


"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."

Ailbek, 1998

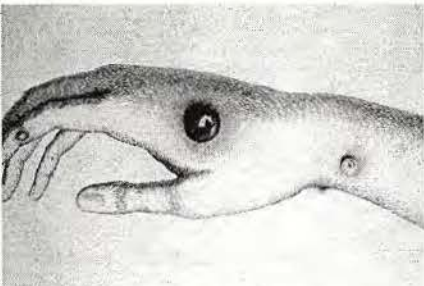
chemical
 survival of viruses
 200 x 10⁶

To appreciate spp - var. / need to know

Milkmaids
 James Phipps - IRP
 Identified even today - one of the greatest discoveries in medicine



Edward Jenner




Cowpox on the hand of Sarah Nelmes

Scarcity of disease - 50%
 American

Smallpox vaccine--landmarks

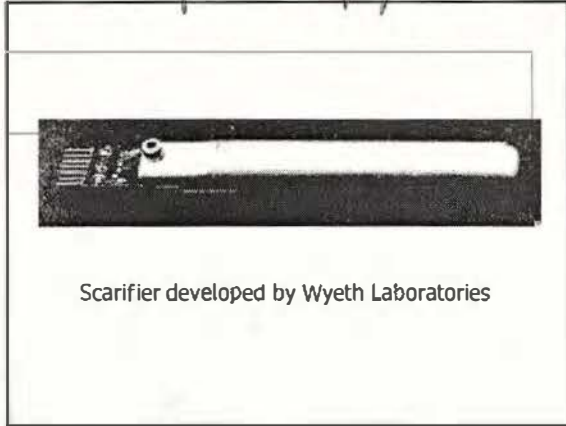
- 1798 - Cowpox, the first vaccine
- Until late 1800s - arm-to-arm spread - 50%
- Late 1800s to 1980 - Usually grown on calves, sheep, water buffalo
 - Two principal strains
 - New York City Board of Health
 - Lister Institute strain



Vaccine collection from cows seeded with vaccinia

↓
 20th century.

Method of prod.
 Create live vaccine that radiated for
 weeks
 stabilizing → the perfect vaccine



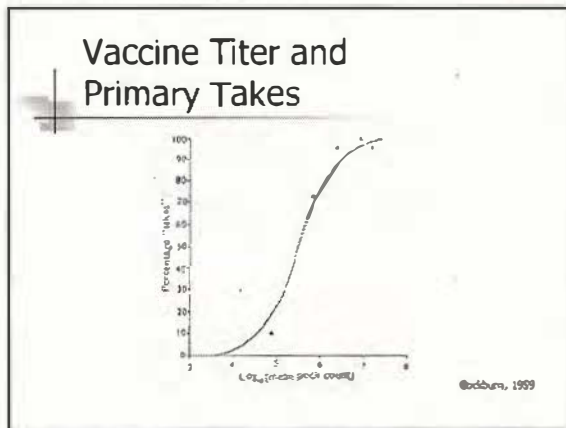
Smallpox Vaccines – International Standards

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

Seed lot system

The "discovery" that vaccine could be diluted 1:15 or 1:10

Many lots.

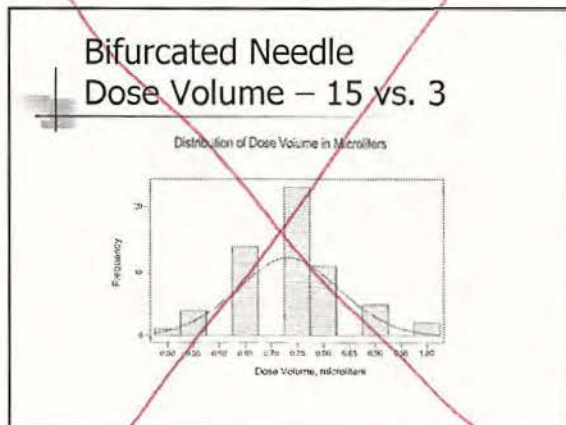
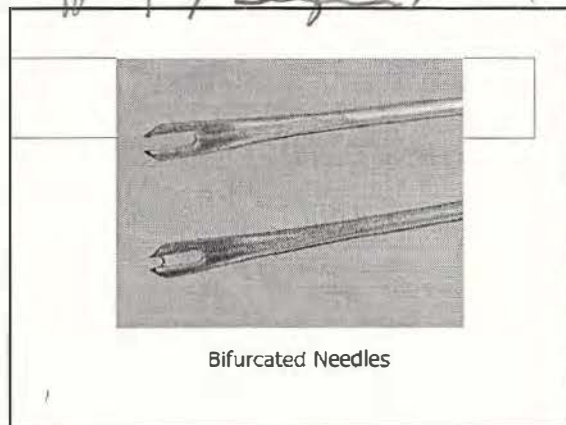


Vaccine Production Laboratories - 1968

	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

one of the great in history
 1966 – Ben Rubin
 Efficiency / ease of use / vaccine x4



1980 – ^{Vaccines stopped} Ended – Vaccine prod stopped –
 Manufacturing plants dismantled.

2000 – No production anywhere. Only vaccine produced in UK + stored ~ 50 million doses

Sept. 11 – D.A. to D.C. Sept 18 – 90,000 doses.

Actin & get mol vaccine -

o Dilution

o Production - Oct. 2001 -

(Amvax rolled vaccine 2000 - \$78/dose - reolyw 2005)

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	

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

— Army + Civ

Aventis Pasteur - "Wetvax" 85 million

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

tested - O.K.

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

No apparent difference in efficacy in reactions

Intravenous Vaccine Immune Globulin --IVIG

- Cangene, a Canadian manufacturer
 - Plasma from paid revaccinated donors
- Sufficient now to treat serious reactions among 40 million vaccinees
- By June, sufficient to deal with 300 million vaccinees

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

Until 4 months ago - vaccine reserved for emergency purposes. U.S. and foreign
 Can outbreak anywhere in a threat,
 One yr. ago - ? what to do to ample vaccine

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

? level of protection

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

Smallpox Vaccine Expected Adverse Events

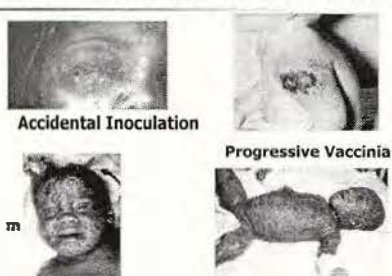
Life-threatening complications	No/million
Post-vaccination encephalitis	2-3
Progressive vaccinia	1-2
Eczema vaccinatum	10-15

- Less serious
 - Rash, fever, accidental inoculation
- If 100 million vaccinated -- 100-400 deaths and some 1500 to 2000 serious complications perhaps requiring hospitalization.

2 cases in 150,000 military personnel

Not pleasant

Vaccination Adverse Events



Accidental Inoculation

Progressive Vaccinia

Eczema Vaccinatum

Progressive Vaccinia

Vaccinia Complications

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

A Balance of Risks

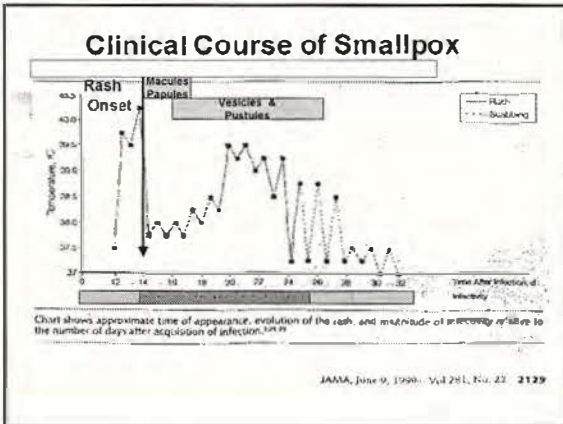
- What is the likelihood that smallpox will be used as a weapon? *Small but not 0*
- What will the frequency of adverse reactions be and how will the public deal with this?

SUPPOSE WE HAD AN EPIDEMIC - 1st POTENTIAL RE: SMALLPOX
 No spread until after illness (like Kyla)
 (is much for branding terrorists)
 30% death rate

Summarize decision -
 course re: compensable (to be dealt with)

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WHO IS AT GREATEST RISK?

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

SMALLPOX DOES NOT SPREAD LIKE A FOREST FIRE

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

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 in special facility until diagnosis is known
- Vaccinate all household contacts of primary contacts (secondary contacts)

NOT ISOLATING

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

BEST APPROACH -

CONTINUE NORMAL ACTIVITIES
AS MUCH AS POSSIBLE

? close schools or work sites -
(6 weeks ??)

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 accommodate 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

letter to say to make available to every county

Adults!
not everyone will - My guess 65%.

Right now - I am beginning to feel more comfortable about our ability to handle a spp outbreak. More comfortable when all regions of the country have completed plans for vaccination if necessary + have plans in hand for caring for 500+ or more casualties.

Key - Don't believe we should or even could live for long periods of time in a state of high tension. Much has been done; more is being done.

You in Nebraska are especially blessed by the leadership shown by your med. etc., the health department, the governor and others in crafting what is clearly one of the best programs in the country. Indeed, we thank them for the model template they offer to the nation.