

Date	Nov 22 2002
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Title	Smallpox vaccines—Then and now
Event	PAHO Technical Advisory Group on Vaccines and Immunization
Event Sponsor	Pan Amer Health Organization (PAHO)
Event location	Washington DC
Notes	This presentation was probably at the PAHO Technical Advisory Group on Vaccines & Immunization immediately preceding the centennial conference (either Nov 22 or 23). The desk diary collapses the 2 speeches into a single entry, citing the TAG as the sponsor for both.
Publ as	

PAHO - 100 + 25%

PAHO
Calle Sir George Aguirre

① Title
~~PAHO~~

in small
manr.

22 yrs. ago - thought we had written last chapter in the spore saga.

Oct 1977 - last case - continuing chain of transmission - 3000 years

May 1980 - WHTA Vaccination stopped + Production ↓

Book - Archival history destined for historical obscurity
smallpox back in the agenda - why

② ~~Dispersal~~

where else smallpox may be - dispersion of sequent. its

Russian labs still secret. If rebound - ~~30% death rate~~ - ~~no immunity~~ - ~~30% death rate~~ - ~~no immunity~~

There is an obvious lesson here - eradication can never be an accepted fact.

Vigilance and a method for dealing with the disease will always be necessary.

That is here and it will be for all time - ~~man kind~~ being what mankind is

- 1st remind you of certain salient aspects of the history of the vaccine
- What is being done re: its possible production + use
- Touchy - possible new vaccines • Surveillance + containment

③ Jenner

James Phipps

④ Had of Sarah Nelson

— arm 15 arm

syphilis, tetanus, hepatitis

⑤ CALVES

Not suitable for tropics until late 1950's - freeze dry

⑥ 1959 1st international standards.

⑦ Why the titer change

1:5 NO SURPRISE

⑧ ~~Why the titer change~~ Many labs. engaged in production

All grown on calves, sheep and water buffalo

Egg - tissue cultures - sterility problem.

Cost per dose 0.5 - 1.5 *

1985 - Vaccine production stopped - labs destroyed.

Vaccine stocks - 1998

60-80 x 10⁶ U.S. 15 x 10⁶

⑨ Bifurcated needles - used in program. Not in indust. countries

TECHNIQUE

⑩ Dose of bifurcated needle. 75/1000 -

Reason for being able to dilute.
dose → 100 → 500

⑪ U.S. Vaccine LICENSURE ISSUE

⑬ ⑭ ⑮ ⑯ ⑰

⑮ VIC

⑮ MVA

⑮ Lcibm8

⑮ Optim for vaccination

⑮ Advers events

⑮ P₀ of advers events

⑮ "A Balance of Risks."

Other countries - product
Vacc. - trail

~~President's decision~~

NOTE PAMP HLB

4
WEB SITE

Smallpox Vaccines – Then and Now



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

Centennial Celebration of PAHO
27 November 2002



"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

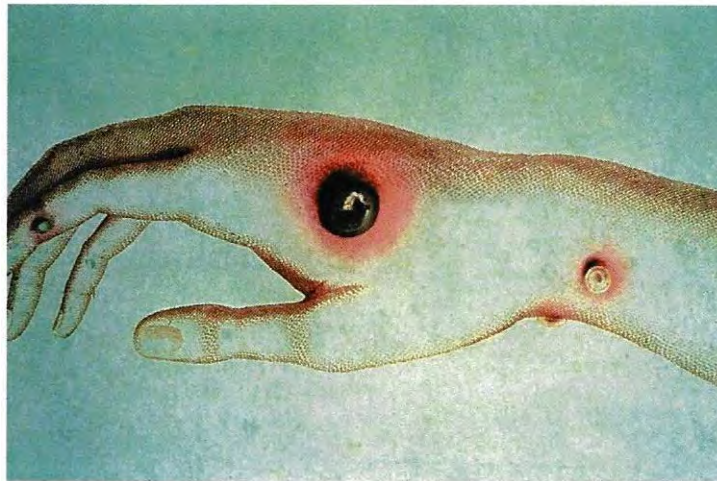


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Edward Jenner

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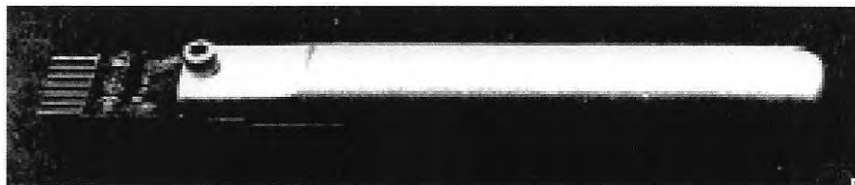
Cowpox on the hand of Sarah Nelmes

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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

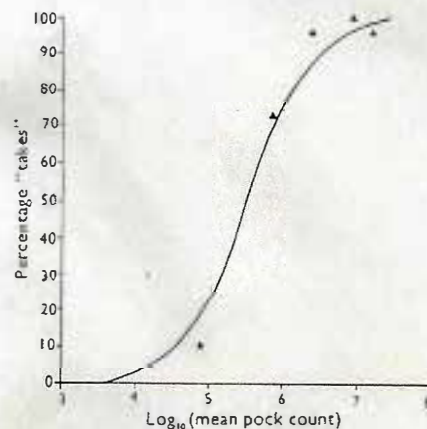
	<u>1959</u>	<u>1965</u>
Titer – pfu/ml	5×10^7	1×10^8
Bacterial count/ml (non-pathogens)	<1000	<500

Seed lot system



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Vaccine Titer and Primary Takes



Cockburn, 1959



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Vaccine Production Laboratories - 1968

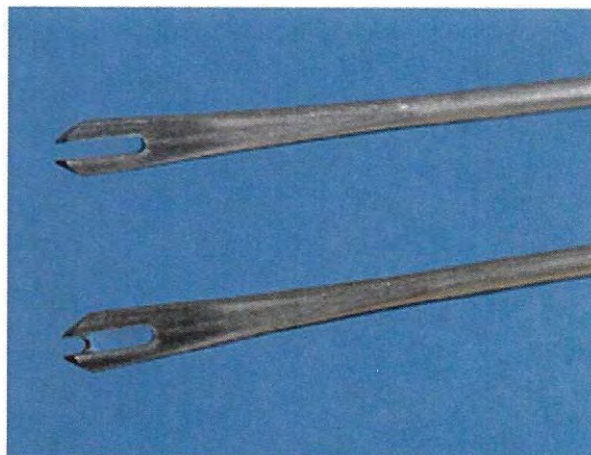
	<u>No.</u>	<u>Strains of Vaccinia*</u>		
		<u>Lister</u>	<u>NYCBOH</u>	<u>Other</u>
Americas	9	2	5	2
Europe	27	8	0	19
Africa	9	3	0	6
Asia/Oceania	19	7	0	12
	64	20**	5	39

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

**By 1971 the number was 39



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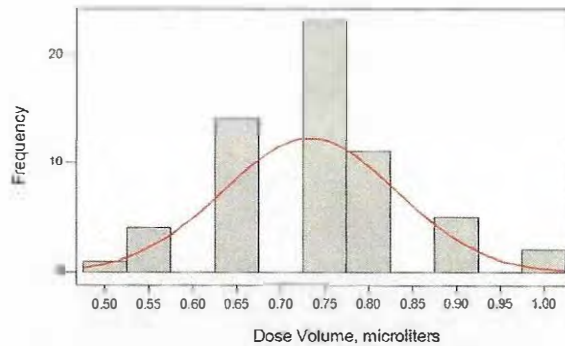
Bifurcated Needles



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Bifurcated Needle Dose Volume

Distribution of Dose Volume in Microliters



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U.S. Smallpox Vaccines

	<u>No. of doses</u>
■ Wyeth DryVax	15 (75) 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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Wyeth DryVax

- NYCBH strain, calf skin, lyophilized
- Currently used for laboratory personnel and plasma donors for VIGIV
- 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

- NYCBH, calf skin, wet frozen, glycerol
- Efficacy and stability studies in progress
- Will remain in IND status
- Emergency (post-event) use only



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ACAM1000

- Contract initiated Sept. 2000 – Acambis
- Seed virus derived from Wyeth seed
- Produced in MRC-5 cells
- Lyophilized, 100 dose vials



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ACAM2000

- Contract in Nov. 2001 – Acambis/Baxter
- Seed virus derived from ACAM1000
- Produced in Vero cells
- Lyophilized, 100 dose vials



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Intravenous Vaccine Immune Globulin

- CDC contract with Cangene, Aug. 2002
 - 30,000 treatment units
 - Plasma from paid revaccinated donors
 - Delivery began in Oct. 2002



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MVA – A Next Generation Vaccine?

- NIH is contracting for development and initial manufacturing of modified vaccinia Ankara (MVA)
- Initial phase I trials planned for this fall under clinical trial agreements with two companies
- Request for Proposal issued – contracts to be awarded January 2003
- Initial purchase contract for up to 30M doses is planned



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Lc16m8 – A Next Generation Vaccine?

- Japanese attenuated strain Lc16m8 should soon be undergoing US trials
- Developed in the 1970s – a temperature-sensitive clone of the Lister strain
- Grown in primary rabbit kidney and has reduced capacity for human skin growth
- Tested in 50,000 Japanese children – less skin reaction and 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
 - Truck drivers
- 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 (may result in blindness)
 - Rash and fever
- If 100 million are vaccinated, 250-400 deaths and 1400 serious, potentially fatal complications are expected



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Vaccination Adverse Events



Accidental Inoculation



Progressive Vaccinia



**Eczema
Vaccinatum**



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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?



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? probability we can control ~~at~~ an outbreak
quickly. Surveillance & containment.
Doris Anderson including NESM, & Ed Kaplan.
European introductions