

Appreciate invitation to be with you at this important meeting and to offer ^{this} honorary address.
~~the world~~ In the troubled times today (facing chemical and biological threats)
 toxicology takes on a new dimension — thank heavens that we have the depth and
 breadth of expertise that you represent. We all hope that we will not ~~again~~ be
 tested — in a civilian setting. But, to a substantial degree, that depends on our

Smallpox: The Death and Resurrection of a Virus

Society of Toxicology

D.A. Henderson M.D., M.P.H.

March 10, 2003



Ali Maalin - 26 October 1977

being prepared
 There is much
 to be done as
 it is a
 different
 world
 from that
 which we
 once —
 not so long ago —
 perceived.

CONTINUING CHAIN / NO ANIMAL



Ramses V

Deaths During the 20th Century

Due directly or indirectly to armed conflict:

100,000,000

Due to smallpox

300,000,000+

ONLY DISEASE WITH DEITIES —

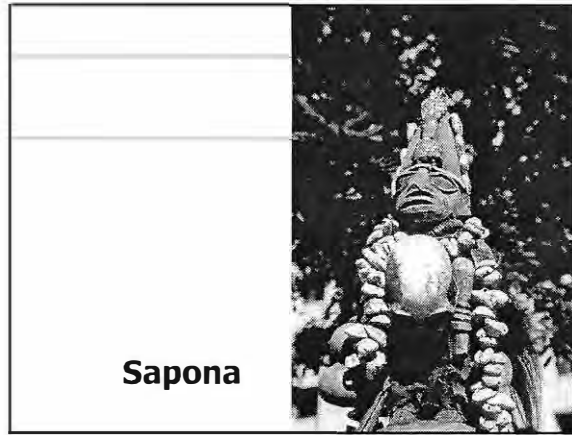
"On May 8, 1980, WHO announced that smallpox had been eradicated from the planet... Soon after the WHO announcement, smallpox was included in a list of viral and bacterial weapons targeted for improvement in the 1981-85 Five-Year Plan.... Where other governments saw a medical victory, the Kremlin perceived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

Alibek, 1998



Sitala Mata

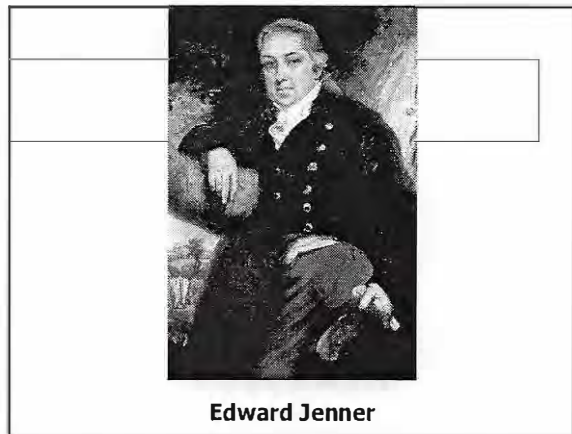
SERGEY POPOV
 SPREAD OF SCIENTISTS



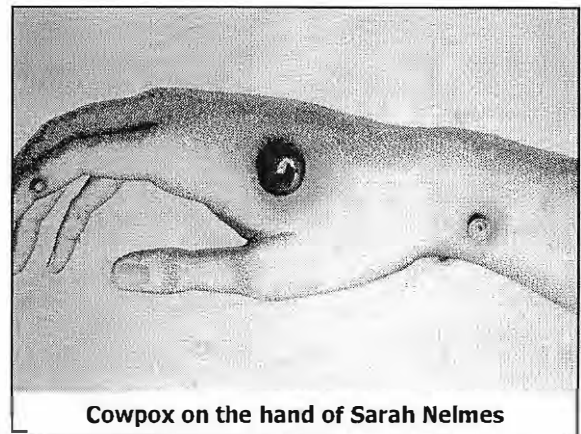
Sapona

"That disease was the most terrible of all the ministers of death. The horror of the Plague...visited our shores only once or twice within living memory but the smallpox was always present, filling the church yards with corpses...and making the eyes and cheeks of the betrothed maiden objects of horror to the lover."

Macauley



Edward Jenner



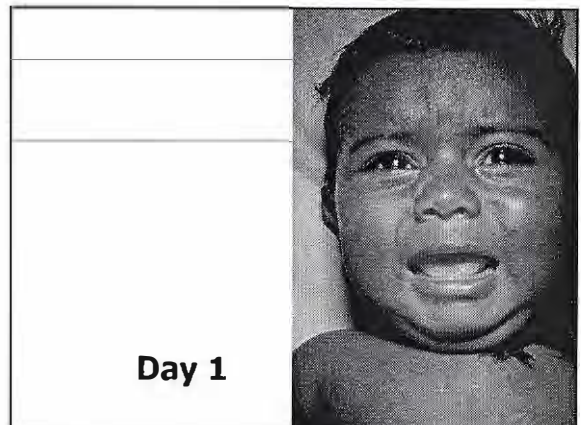
Cowpox on the hand of Sarah Nelmes

WHAT ABOUT THE DISEASE ITSELF

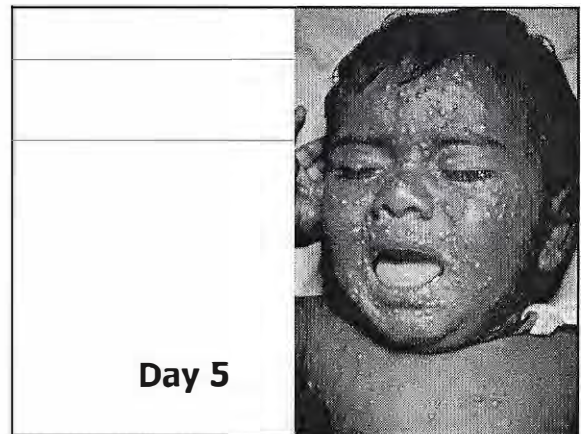
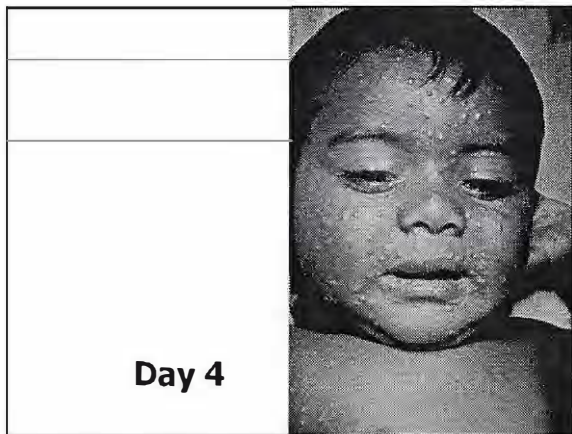
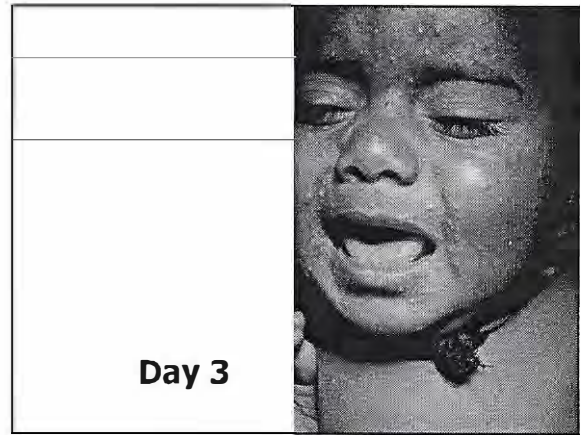
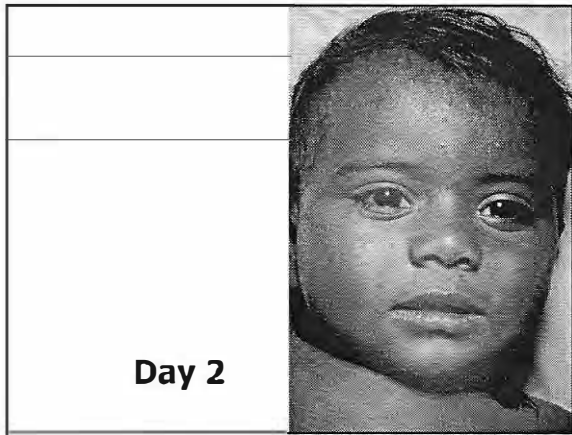
1st VACCINE & ONE OF GREATEST DISCOVERIES

Facts About Smallpox

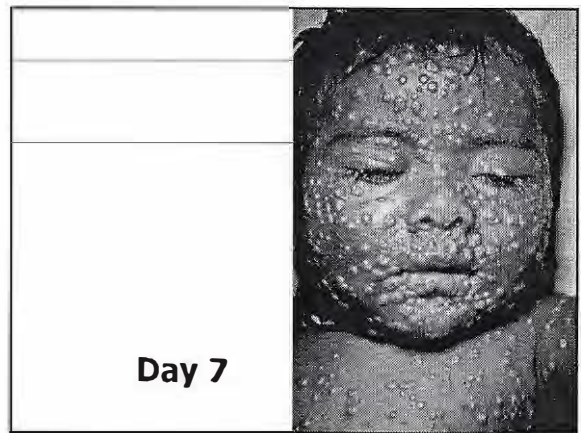
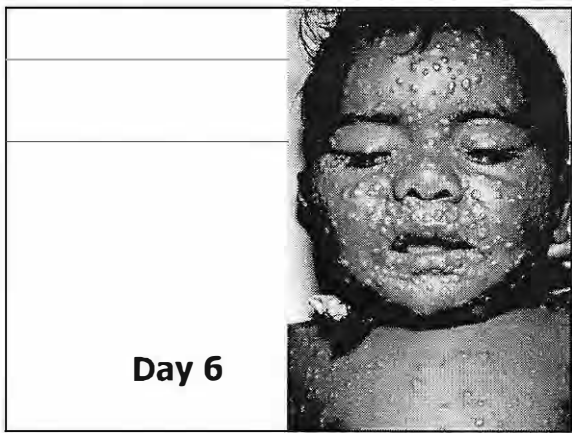
- Time between infection and illness 12 days
- Fever, flu-like symptoms then rash
- Case fatality rate --30 %
- Not infectious until ill with fever and rash
- Transmission affected by temp and humidity
 - Summer: Low
 - Winter: High (3 to 4 fold higher)

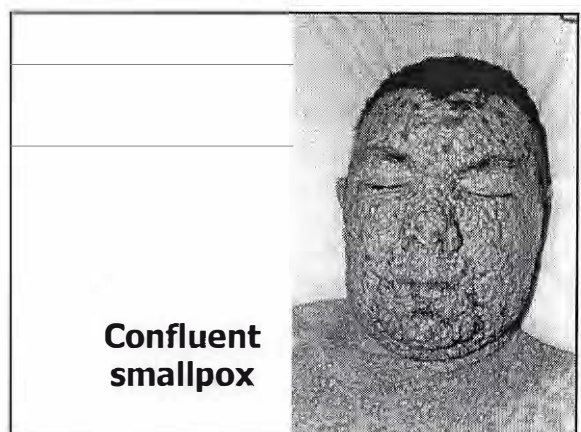
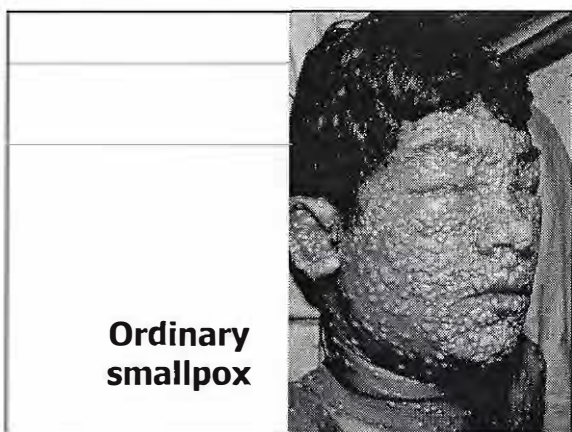
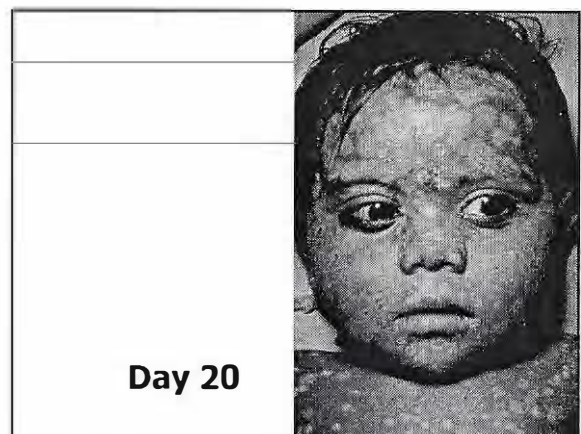
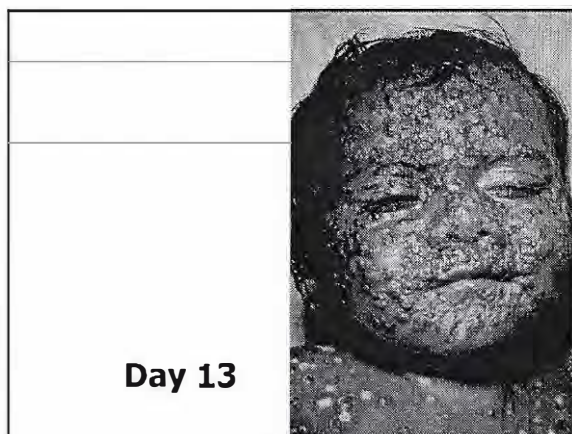
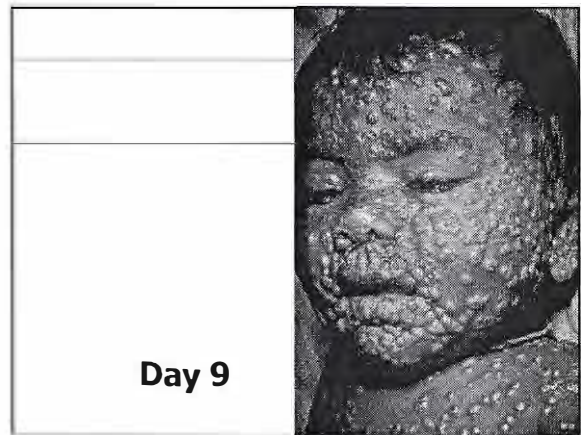
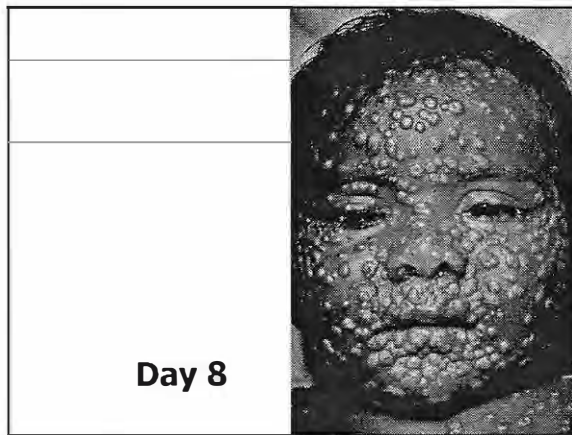


Day 1



~~ERUPTIVE~~ - TROUBLE EATING/DRINKING



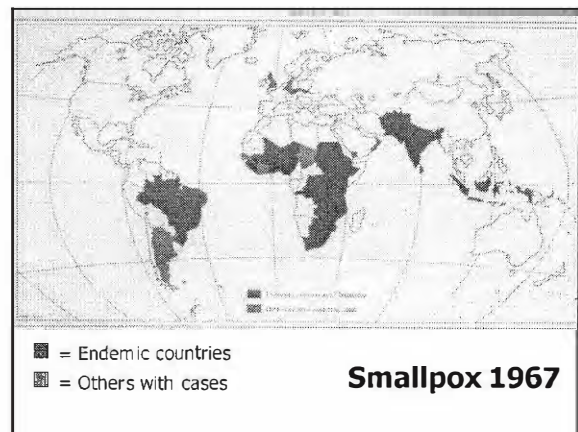




1966 - Decision to start eradication

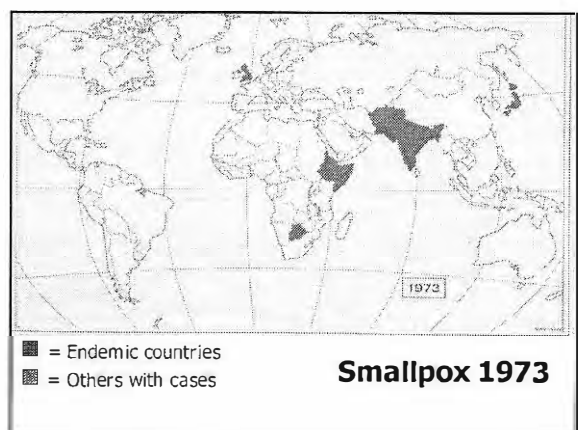
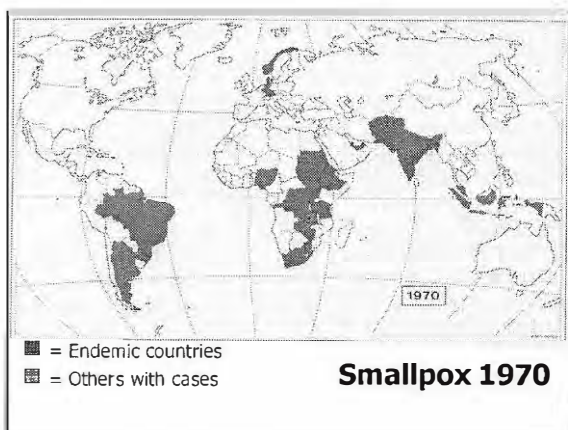
Characteristics of Smallpox Favoring Eradication

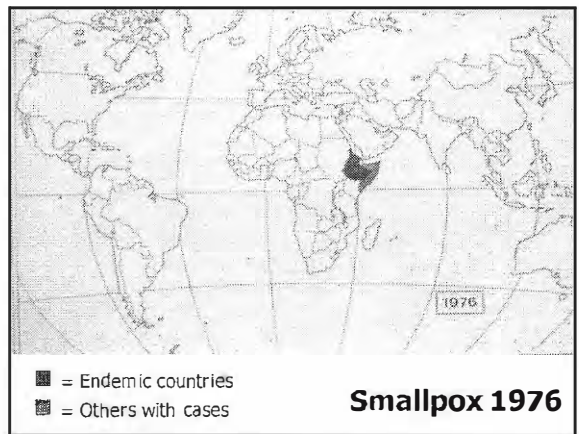
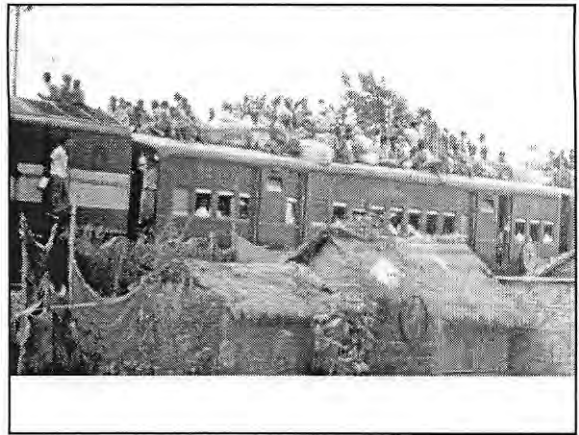
- Man -- the only host
- Virus transmission- only during rash
- Permanent immunity after recovery
- Spread of virus during face-to-face contact
- Transmission stopped spontaneously in remote areas
- Vaccine provided long-lasting protection



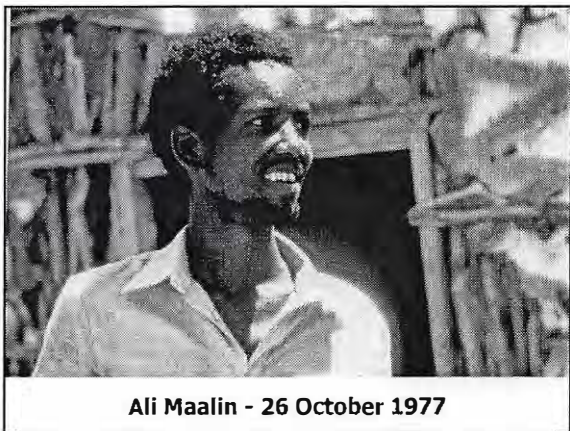
+ VACCINE - ONE DOSE

STRATEGY





ONE TROUBLING OUTBREAK

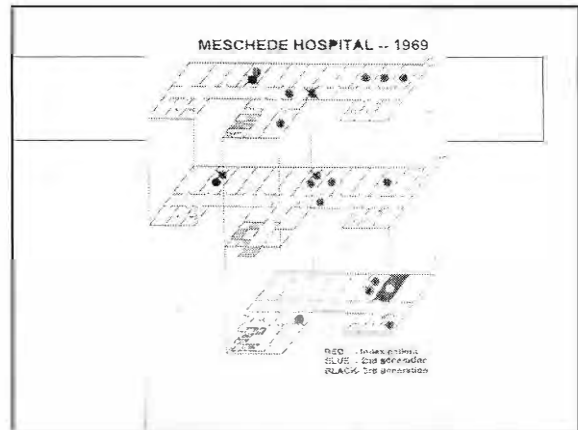
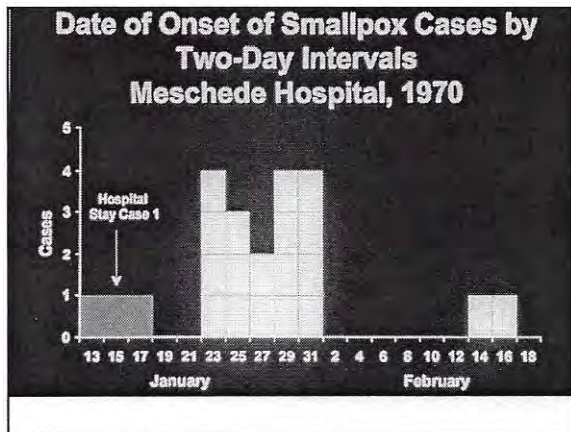


Ali Maalin - 26 October 1977



Meschede, Germany - January 1970

CONGIA



SEPT. 18 - 90 000 doses
18 months ago.

Susceptibility of US Population to Smallpox -- 2003

- Vaccination stopped in 1972
- Few under 32 years of age have been vaccinated -- 45% of the population
- Americans vaccinated only once before 1972 have limited immunity- about 35% of population

U.S. Smallpox Vaccines

	No. of doses
■ Wyeth DryVax	15 (75) million
■ Manufactured 1978	
■ Aventis Pasteur	85 million
■ Manufactured 1958	
Acambis/Baxter	209 million
■ Vero cell production	

No vaccine production anywhere in the world.

Wyeth DryVax

15 million

- NYCBH strain, calf skin, lyophilized
- Licensed
- 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

Aventis Pasteur

85 million

- NYCBH, calf skin, wet frozen, glycerol
- Not licensed -- IND status
- Emergency use only
- 100 dose vials: can be diluted 5:1

ACAM 2000

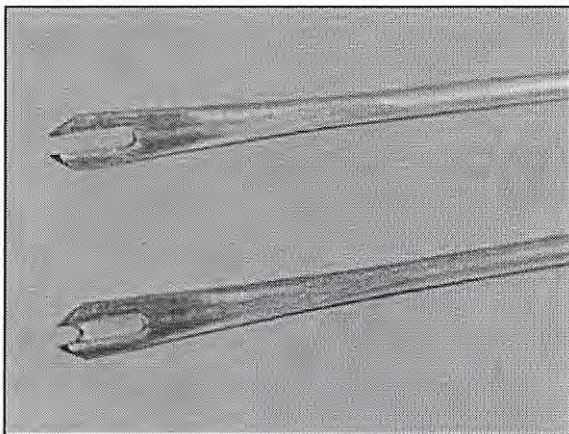
209 million

- Acambis/Baxter
- Seed virus -- Wyeth seed (NYCBH)
- Produced in Vero cells
- Lyophilized, 100 dose vials
- Licensure – early 2004

Intravenous Vaccine Immune Globulin

Produced by Cangene, Canada

- 40,000 treatment units
- Plasma from paid revaccinated donors
- Sufficient now to treat expected serious reactions among 40 million vaccinees
- By June, sufficient for 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 NYCBH vaccinia
- Contract awarded for development and initial manufacturing
- Phase 1 trials are in progress

Lc16m8 – A Next Generation Vaccine?

- Temperature-sensitive clone of Lister strain develop in Japan in the 1970s
- Trials to begin soon in U.S. 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

Options for Vaccination Before an Event

- ~~Vaccinate no one~~
- Vaccinate those at highest risk, candidates:
 - Health care workers
 - First responders
 - Truck drivers
 - Essential personnel
- ~~Vaccinate anyone~~ desiring to be vaccinated
 - Recommend vaccination
 - Recommend against vaccination
- Make ~~vaccination~~ compulsory

last Spring - confident enough vaccine by fall.
What to do?

8

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, 100-400 deaths and 2500 serious, potentially fatal complications are expected

Vaccination Adverse Events



Accidental Inoculation



Progressive Vaccinia



Eczema
Vaccinatum



where today

7-250000

5 mod. serious

Contact Vaccinia Infection

Source of Vaccinia (1963-68 studies)

Age of infected patients	Siblings/ playmates	Parents/ close relatives	Son/ daughter/ grandchild	Other
0-4	75	11	0	5
5-19	21	2	0	1
20+	1	0	24*	3
Total	97**	13	24	9

*Primarily parents and grandparents

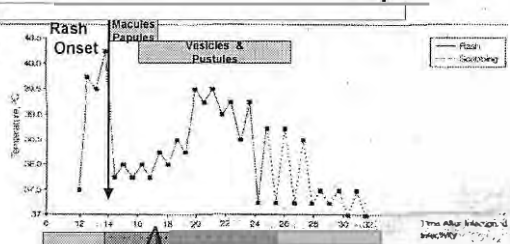
**81 siblings; 16 playmates

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 a risk-averse public deal with this?
- How effectively could we control an outbreak?

Recommendation today - only those at high risk

Clinical Course of Smallpox



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

vaccination up to 3-4 days after

Spread of Infection

Spread of disease is comparatively slow

- Household spread** -- Secondary attack rates
 - Measles 76%
 - Chickenpox 74%
 - Smallpox 58%
- Community spread** -- measles and chickenpox spread even before symptoms; smallpox does not

Epidemiology of Smallpox

Transmission Patterns in Europe: 1958-1973

- Outbreaks: 34
- Cases: 573
 - Transmission in hospital: 277 (48%)
 - 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 cases
 - Jun to Nov 10 importations average + 0.5 cases

Surveillance and Containment

Steps in Containment

- Vaccinate and isolate patient in designated hospital or ward
- Identify and 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 temperature
 - If a primary contact develops fever, isolate at home or special facility until diagnosed
- Vaccinate all household contacts of primary contacts (secondary contacts)

smallpox outbreak, were it to occur, would be a challenge - as much, I believe, because of the alarm it would generate, as the cases that would ensue!

Vaccine - available in 12 hours anywhere.

H.D. - now planning ~~to~~ to make vaccine widely available quickly

Keop. system - plans for > 500 patients.

~~18 months ago~~

We are infinitely better prepared than we were 18 months ago.

More to be done - no question but I personally sleep much better at night.

However, the threat of these weapons is now with us. I see no prospect of ever putting the genie back in the bottle. But this is a problem that we can handle, working together.