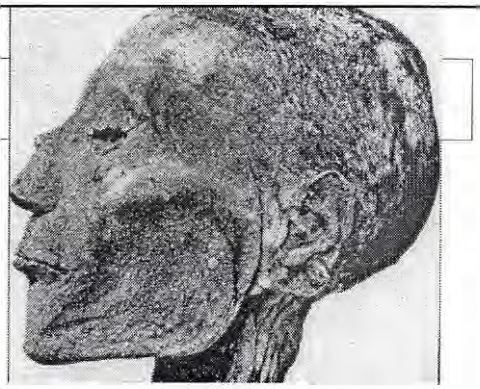
The Smallpox Saga: still unwritten chapters

American Society for Microbiology

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

May 18, 2003

Ali Maalin - 26 October 1977



Ramses V

Deaths in the 20th Century

Due directly or indirectly to armed conflict:

100,000,000

Due to smallpox

300,000,000+

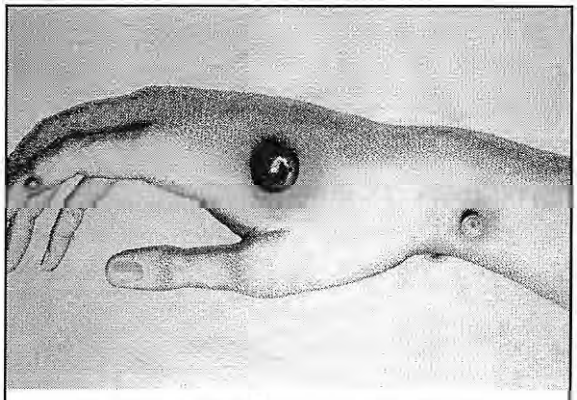
Sitala Mata

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 churchyards with corpses...and making the eyes and cheeks of the betrothed maiden objects of horror to the lover."

Macauley

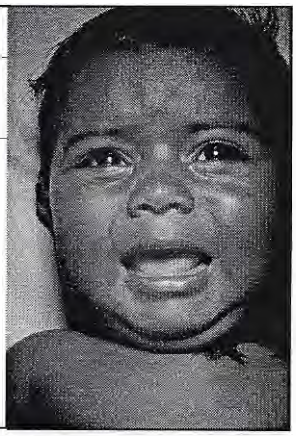
Edward Jenner



Cowpox on the hand of Sarah Nelmes

Smallpox -- characteristics

- Time -- infection to illness is 12 days
- Fever, flu-like symptoms then rash
- No anti-viral therapy available
- Case fatality rate --30 %
- Not infectious until ill with fever and rash



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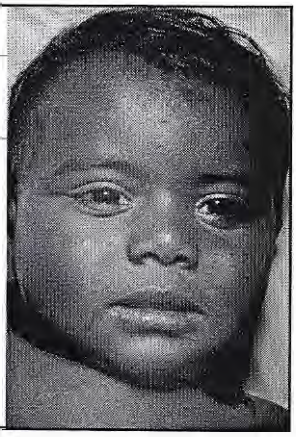

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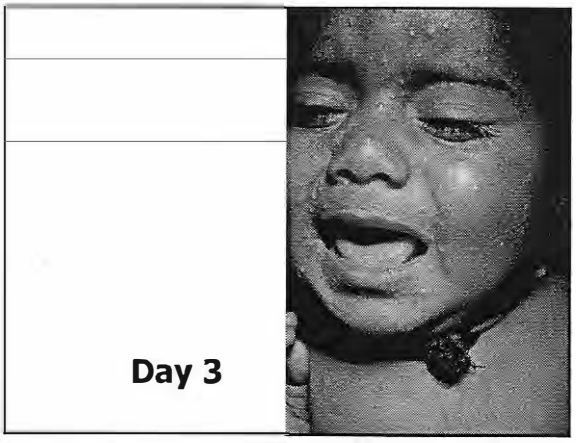

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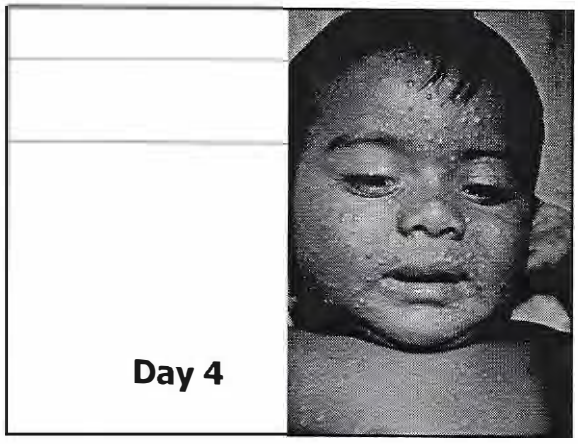

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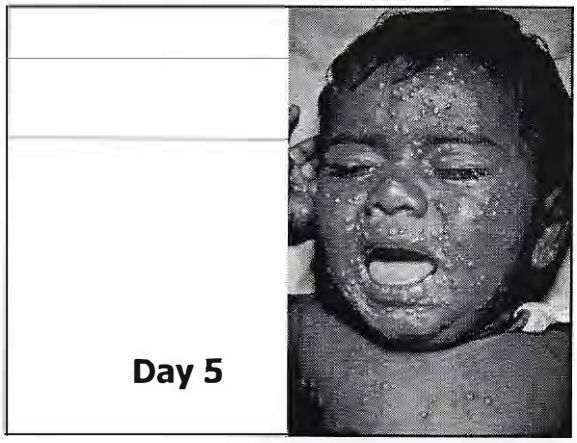

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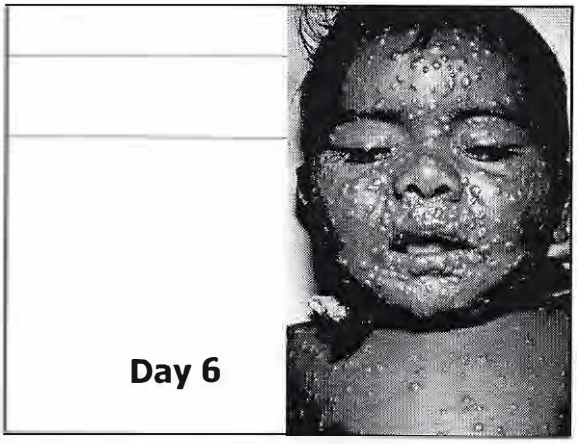

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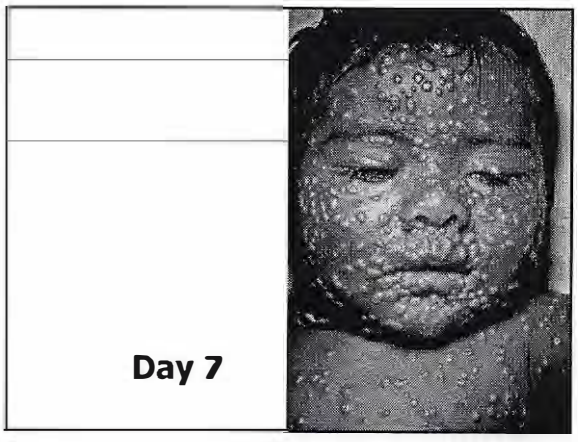

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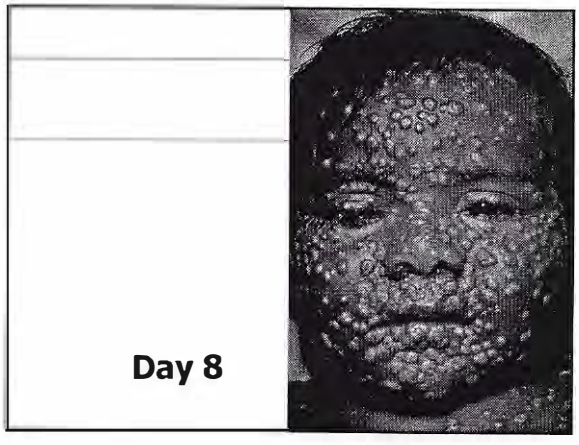

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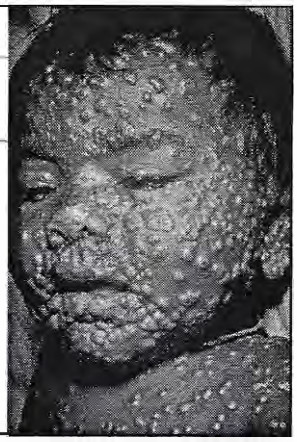
Day 9

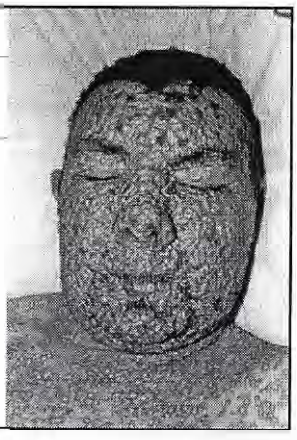


Day 13

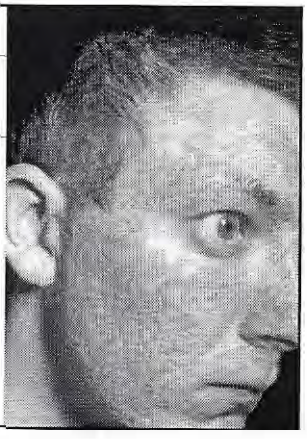
Day 20

Ordinary smallpox

Confluent smallpox

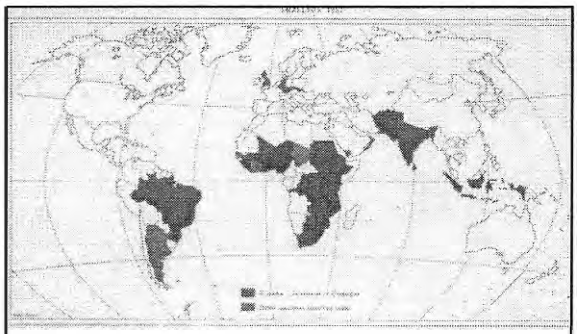


Confluent smallpox (recovered)



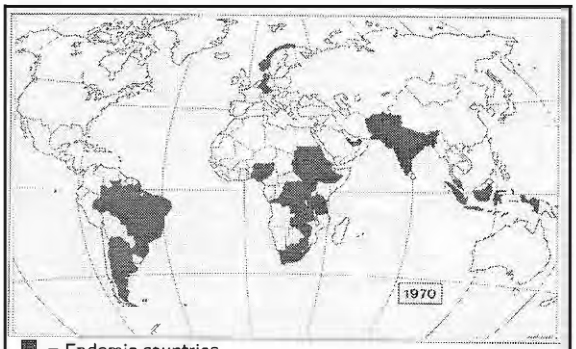
Characteristics of Smallpox Favoring Eradication

- Man -- the only host
- Virus spread -- only during rash
- Permanent immunity after recovery
- Spread of virus by face-to-face contact
- Transmission stops spontaneously in remote areas
- Vaccine provides long-lasting protection



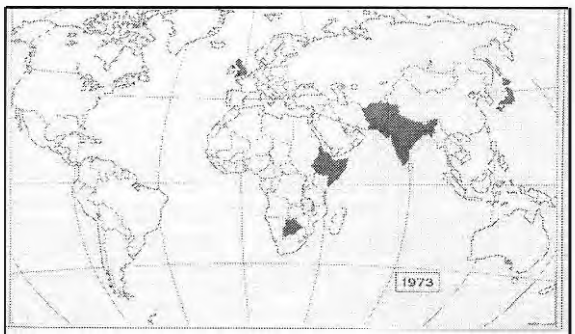
= Endemic countries
= Others with cases

Smallpox 1967



= Endemic countries
= Others with cases

Smallpox 1970



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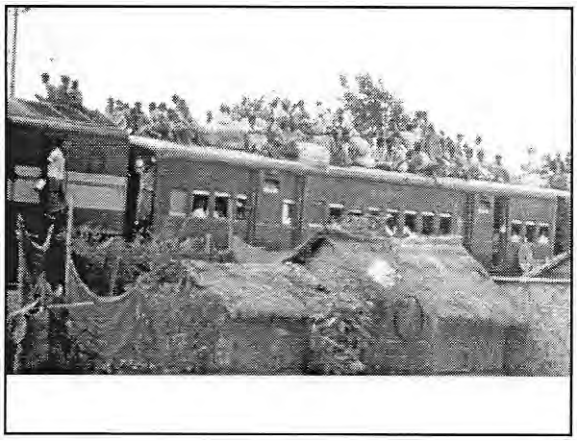
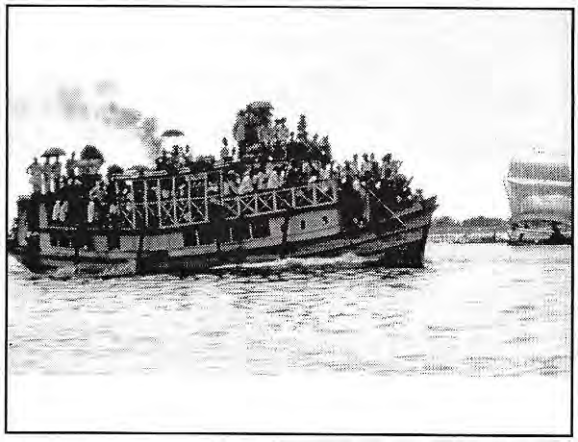
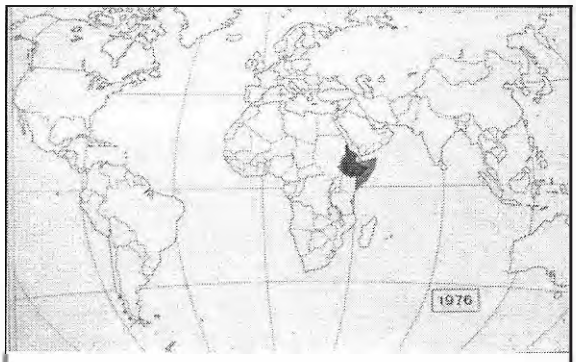
Smallpox 1973





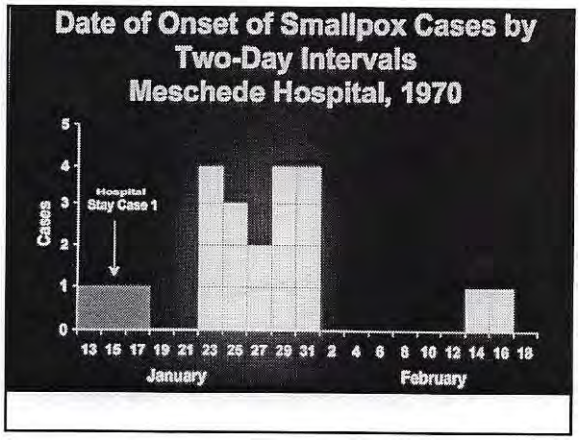


■ = Endemic countries
▩ = Others with cases

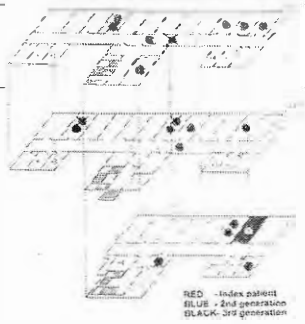
Smallpox 1976

Ali Maalin - 26 October 1977

Meschede, Germany - January 1970



MESCHEDE HOSPITAL -- 1969



"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

Susceptibility of US Population to Smallpox -- 2003

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

Epidemic Response Capability

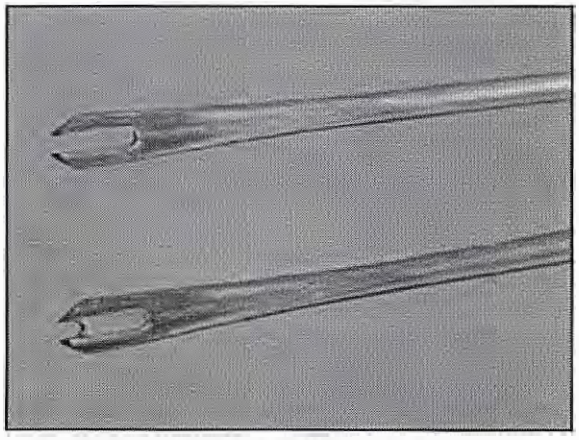
September 18, 2001

- Vaccine manufacturers
  - U.S. None
  - World None
- Vaccine in storage
  - U.S. 15 million doses
  - World ? 80 million doses
- Ready for emergency shipment
  - 90,000 doses of vaccine
  - Limited quantities – needles, VIG

U.S. Smallpox Vaccines

	No. of doses
Wyeth DryVax	15 million
Calf-lymph - 1978	
Aventis Pasteur	85 million
Calf-lymph - 1958	
Acambis/Baxter	209 million
Vero cell - 2002	

In emergency – dilution of vaccine 1:5 is possible



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**

A Balance of Risks

- Probability that smallpox will be used as a weapon
- Frequency of adverse reactions and public response in 2003
- Likely effectiveness of outbreak control?

Smallpox Vaccine Expected Adverse Events

- **Life-threatening complications (per million)**
  - **Post-vaccinal encephalitis (3)**
  - **Progressive vaccinia (1)**
  - **Eczema vaccinatum (12)**
- **Less serious**
  - **Generalized vaccinia**
  - **Accidental inoculation**
  - **Rash and fever**
- If 100 million vaccinated, 100+ deaths might occur (1960's data)

Smallpox vaccine Experience to date*

- Numbers are still small – 475,000
  - **Post-vaccinal encephalitis - 1**
  - **Progressive vaccinia - 0**
  - **Eczema vaccinatum - 0**
- Generalized vaccinia - 39
- Infection in contacts - 21

*Note: data are provisional

Smallpox vaccine
Cardiac complications

- Myopericarditis 32*
  - Onset 7 to 17 days
  - Fever, chest pain, EKG changes, enzymes increased
  - Recovery
- Ischemic events 10*
  - Angina, myocardial infarct
  - Difficult to distinguish from normal background
  - Almost certainly coincidental

*Note: data are provisional

Outbreak control

- Smallpox doesn't spread readily
- Patient transmits only after symptoms
- Vaccine protects even when given 3-4 days after infection
- Models in progress

Clinical Course of Smallpox

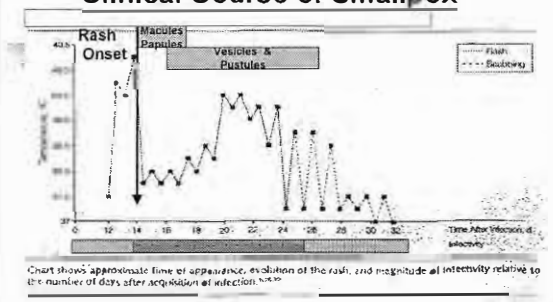


Chart shows approximate time of appearance, evolution of the rash, and magnitude of infectivity relative to the number of days after acquisition of infection.

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

Spread of Infection

Spread of disease is slow

- **Household spread --Secondary attack rates**
  - **Measles76%**
  - **Chickenpox 74%**
  - **Smallpox 58%**
- **Community spread –measles and chickenpox spread 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 -- I

- **Vaccinate and isolate patient**
- **Identify and vaccinate all persons who had been in a room with the patient since he/she became febrile (primary contacts)**
- **Place primary contacts under surveillance with twice daily temperatures**
  - **If the contact develops fever, isolate at home or special facility until diagnosed**
- **Vaccinate all household members of primary contacts (secondary contacts)**

Surveillance and Containment

Steps in containment -- II

- **Make vaccine available on request to those in the area**
- **Communicate with public and professionals frequently and promptly (anticipate CNN)**
- **Not generally desirable:**
  - **Compulsory vaccination**
  - **Quarantine of city or groups of people**
  - **Closure of airports, suspension of transport**

Preparatory steps -- in progress

- Vaccine –
  - Stockpiled--available anywhere in 12 hours
- Each metro region to have plan to make vaccination widely available over 7-10 days
- Each metro region to have plan to accommodate 500+ patients per million pop.
- Every ER to have negative pressure rooms for examining rash and fever patients

- Are we now better prepared than on 9/11 ?
- Are we fully prepared ?
- How long must we sustain our efforts ?

- Other chapters remain to be written
- May they be few and and brief