

The Death and Resurrection of a Virus

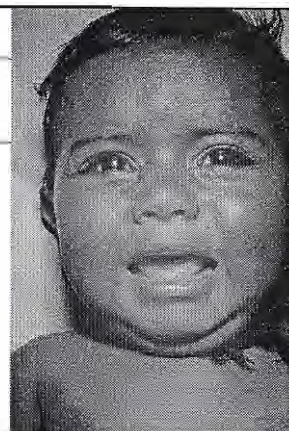
D.A. Henderson MD, MPH

Grand Rounds

Stony Brook, Long Island

March 16, 2005

Day 1



Day 2



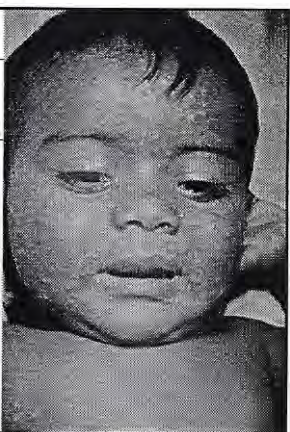
Diff Dx Dengue, a. pox

Day 3



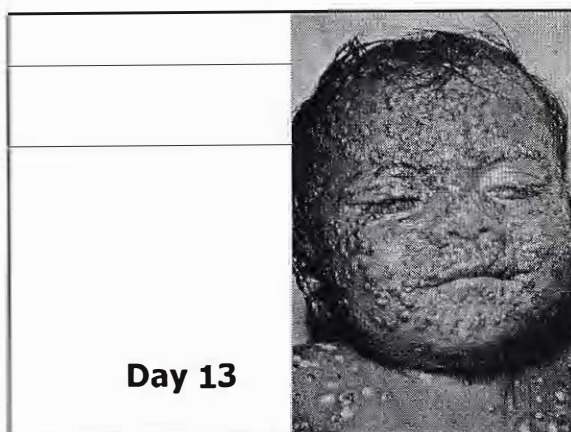
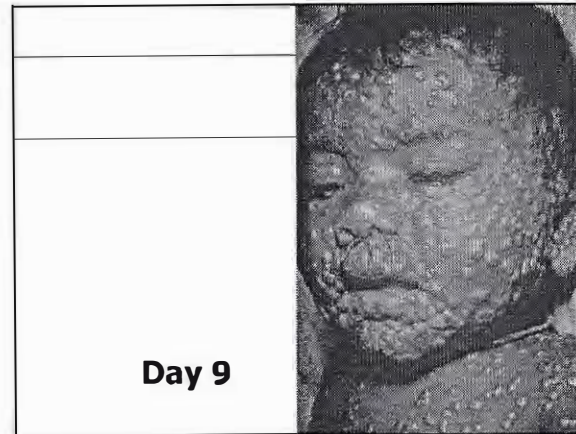
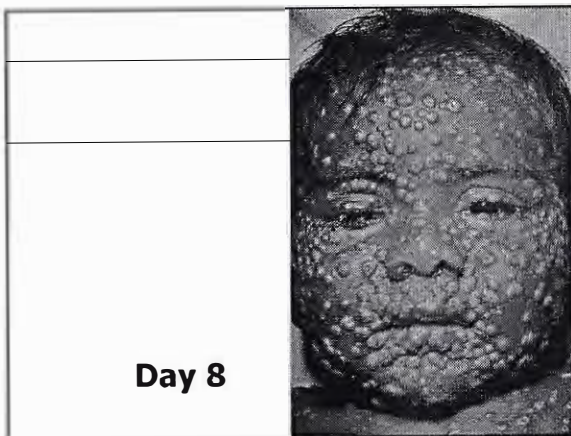
pharyngeal lesions

Day 4

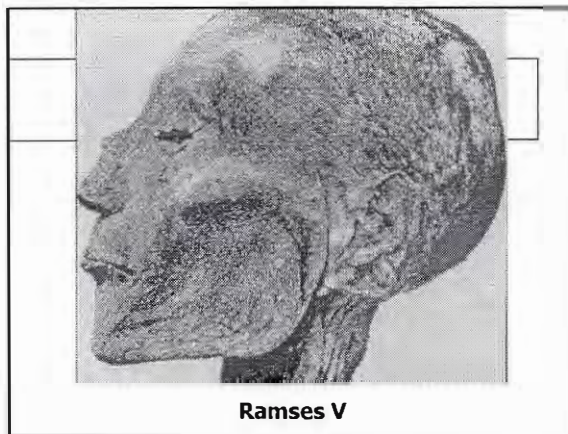
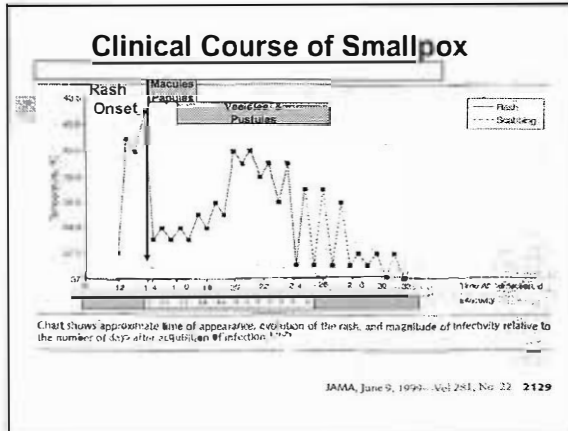


Day 5



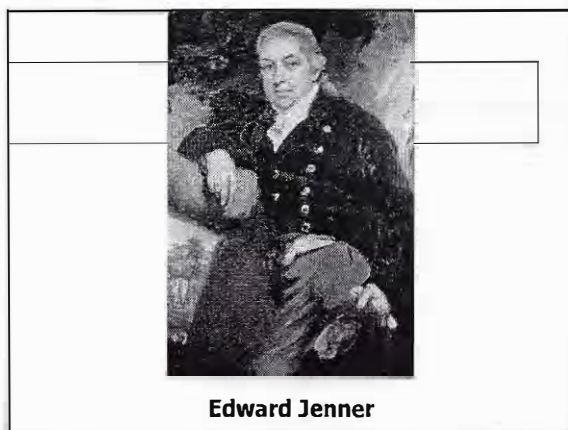


Smallpox -- characteristics <i>contagious / lesions down slope of face</i> ▪ Incubation period is 10-12 days ▪ Severe flu-like symptoms then rash ▪ Case fatality rate --30 % ▪ No therapy available
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"That disease was the most terrible of all the ministers 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



Deaths in the 20th Century

Due directly or indirectly to armed conflict:

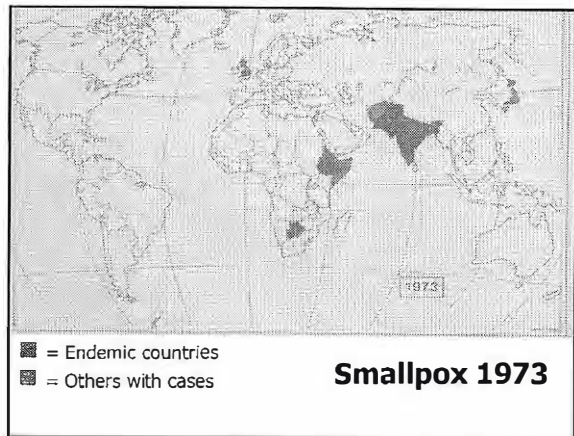
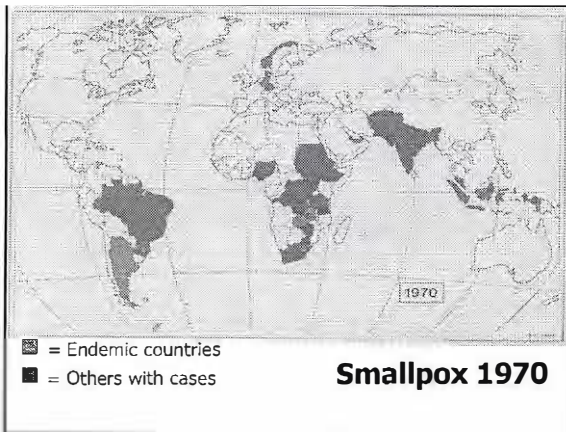
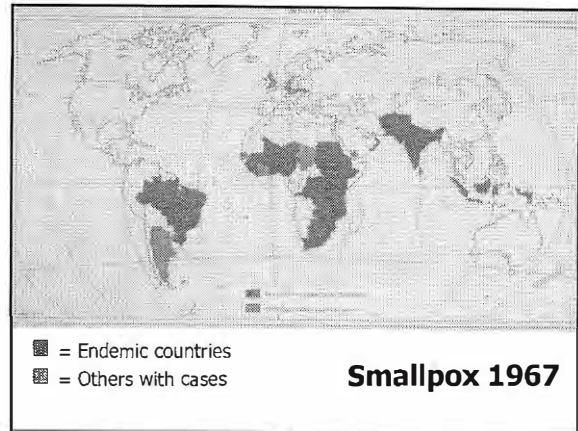
100,000,000

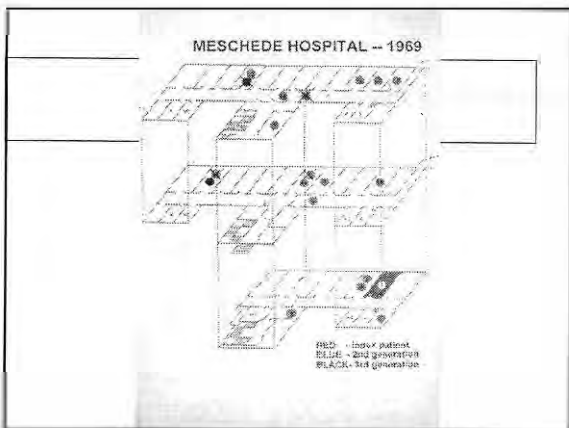
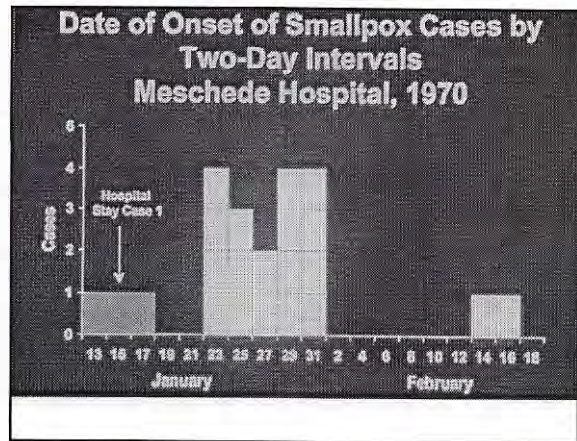
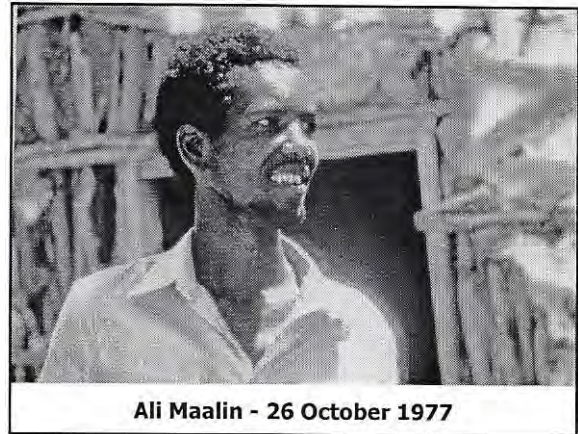
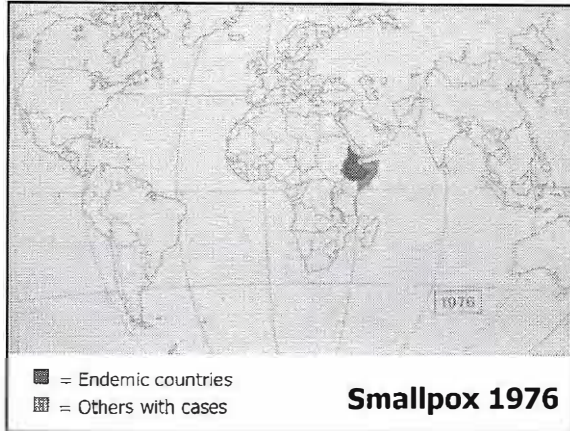
Due to smallpox

300,000,000+

Characteristics of Smallpox Favoring Eradication

- Man -- the only host
 - Virus spread -- only during rash; face-to face contact
 - Permanent immunity after recovery
 - Transmission stops spontaneously in remote areas
 - Vaccine is heat-stable and easy to administer
- One dose provides long-lasting protection





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.... Soviet military command issued an order to maintain an annual stockpile of 20 tons."

Ken Alibek, 1998

- "In December 1990, testing of the new large-scale reactor formulation (630 Liters) was completed. The weapon was ready to be accepted in armament."

Ken Alibek, 2003

The Soviet Threat

- Bioweapons Program
 - Unknown until 1989
 - 60,000+ persons in 50 laboratories
- More than half of scientists no longer engaged – international dispersal
- Major smallpox production lab (Sergiyev Posad)—still a secret facility

Locations of smallpox virus -- 2004

- Known stocks of smallpox virus
 - Centers for Disease Control, Atlanta
 - Russian State Research Center of Virology, Novosibirsk
- Russian centers for smallpox virus production
 - Sergiyev Posad, Kirov, ?other
- Other countries
 - ?Retained stocks from 1970s
 - ?Virus and/or expertise from former Soviet labs

Susceptibility of population to smallpox -- 2005

- Vaccination stopped by 1980
- No persons under 25 years have been vaccinated
- Persons vaccinated only once pre-1980 have little or no immunity
- General population— probably 75% are fully susceptible to smallpox

Vaccine availability -- 2001

- Vaccine manufacturers
 - U.S. None
 - World None
- Vaccine in storage
 - U.S.— 9/16 90,000 doses
 - 12/31 15 million doses
 - WHO 2 million doses
 - World ? 80 million doses

A Balance of Risks

- Probability that smallpox will be used as a weapon
- Frequency of adverse reactions
- 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 vaccination Military experience*

- Total screened 757,000
- Total vaccinated 708,500 (94%)
 - Post-vaccinal encephalitis - 1
 - Progressive vaccinia 0
 - Eczema vaccinatum 0
- Infection in contacts - 49
- Doses of VIG used 3

*As of 1 December 04

Smallpox vaccine Cardiac complications --military

- Myopericarditis 84
 - Onset 7 to 17 days
 - Fever, chest pain, EKG changes, enzymes increased
 - Recovery
- Ischemic events 24
 - Expected (age adjusted) 40

Outbreak control

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

Spread of Infection

Spread of disease is slow

- **Household spread** --Secondary attack rates

Measles	76%
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

Surveillance and Containment

Steps in Containment

- Isolate patient
- Vaccinate all persons who had been in a room with the patient since he became febrile
 - Place them under surveillance with daily temperatures and isolate if fever develops
 - Vaccinate their household contacts
- Make vaccine available on request to those in the area

Vaccination policy

tumultuous debate thro 2003

- Public demand
 - Unions – first responders, pilots, nurses
- White House and Homeland Security
- OPHEP – need to educate
- A 3 step approach decided
 - Highest risk –hospitals, public health-500K
 - First responders – 10 million
 - Public who desire vaccine

The Vaccination Program collapses

- No smallpox or WMD found in Iraq
- Personal concerns about complications
- Liability issues remained unresolved
- No provision to reimburse health departments for costs
- Military reports cases of myopericarditis
- The program unofficially draws to a close with some 40,000 vaccinated

Where do we go from here?

- Vaccine use policy
 - Continue to try to get health care workers vaccinated?
 - Should vaccine be made available to anyone who wants it?
- New vaccines
 - How might they be used?

MVA – Next Generation Vaccine?

- Non-replicating attenuated vaccinia strain (Modified Vaccinia Ankara)
- Good antibodies; protects monkeys
- 400 vaccinated – minimal reactogenicity
- Vaccination– 1 or 2 doses
- Manufacturing to begin in next 6 months
- Cost (est.) -- \$20 per dose

Lc16m8—Next Generation Vaccine?

- Japanese attenuated replicating strain from Lister strain -- grown in rabbit kidney cells
- Good antibodies; protects monkeys
- 150,000 Japanese children vaccinated – minimal reactogenicity
- Manufacturing already in progress
- Cost (est.) –probably \$2 per dose



The future

- The threat will not go away
- With adequate supplies of vaccine and an ability to act quickly, a smallpox release can be readily managed
- International cooperation, especially communication and action, are vital
WHO must be given the lead and assume it

6 month old Pakistani boy, Rashid

contact - small case in
hospital ward - no bed open

~~1~~ 1 February high fever, vomiting, crying constantly. Temp 38.5
Nurse exam. Nothing remarkable found - lungs clear, abdomen soft.

no evidence of abscesses, mucous membranes clear.
~~Diagnosis~~ Mother reassured - given vitamin preparation,
has had a convulsion in

OPD. (hosp.) 2 February - Child in obvious distress; Temp is 40°C; ~~exam~~
No localizing signs.

Blood work up shows slight Leukopenia

P.E. unremarkable

~~no~~ few macules
erupted.

Admitted for observation.

GRANDS ROUNDS - JH. - if a red case
~~the~~ were presented -