Smallpox

Center Seminar

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February 15, 2005

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Ali Maalin - 26 October 1977

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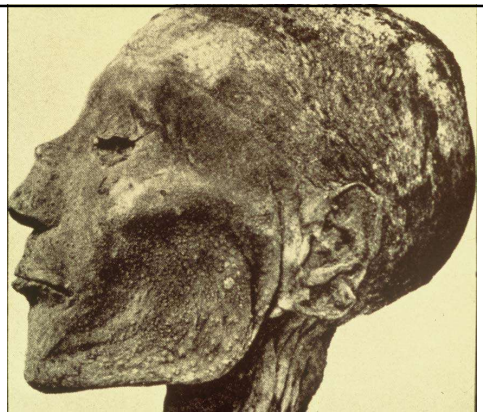

Ramses V

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Deaths in the 20th Century

Due directly or indirectly to armed conflict:

100,000,000

Due to smallpox

300,000,000+

4

"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

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Edward Jenner

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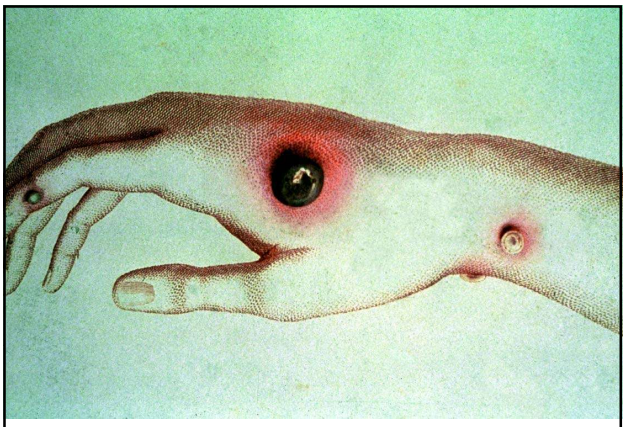


Cowpox on the hand of Sarah Nelmes

7

The Smallpox Virus

- Family – *Poxviridae*
  - Includes monkeypox, cowpox, vaccinia
- DNA virus – largest of all virions
- Man is the only host

8

Epidemiological factors

- Virus spread -- only during rash
- Spread by face-to-face contact
- Permanent immunity after recovery
- Marked seasonal fluctuation
- Transmission stops spontaneously in remote areas

9

Smallpox – clinical characteristics

- "No" sub-clinical infections
- Incubation period – 7 to 17 days
- Fever, flu-like symptoms then rash
- No anti-viral therapy
- Case fatality rate --30 %

10

Clinical Course of Smallpox

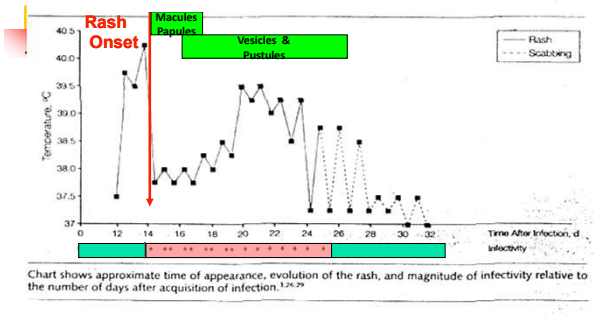
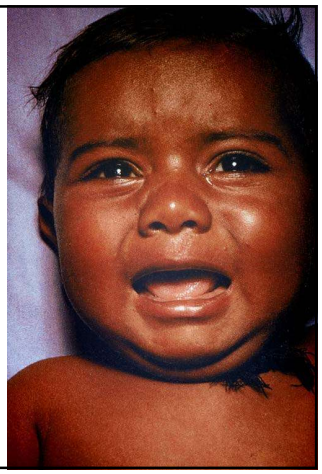


Chart shows approximate time of appearance, evolution of the rash, and magnitude of infectivity relative to the number of days after acquisition of infection.[1,24,29]

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

11



Day 1

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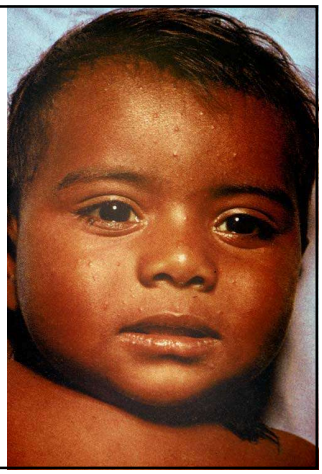
Day 2



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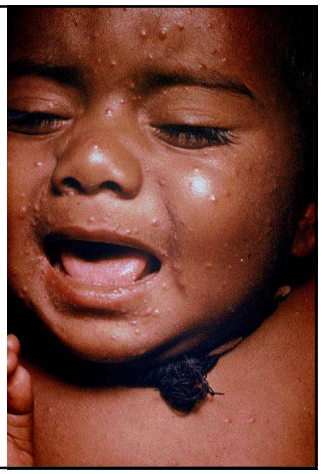

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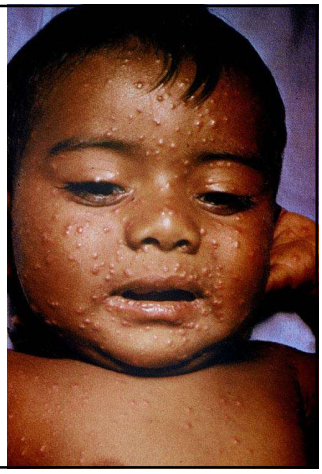

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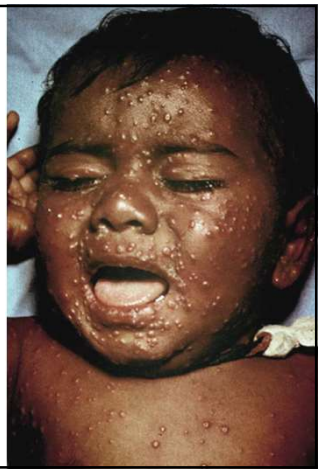

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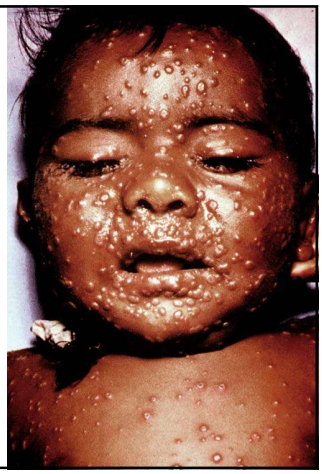

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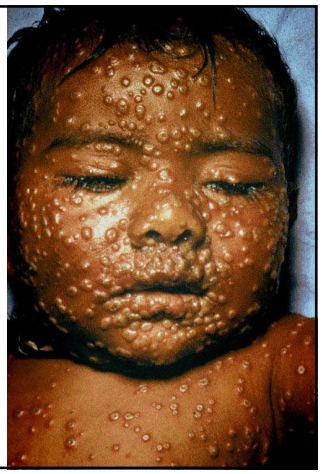

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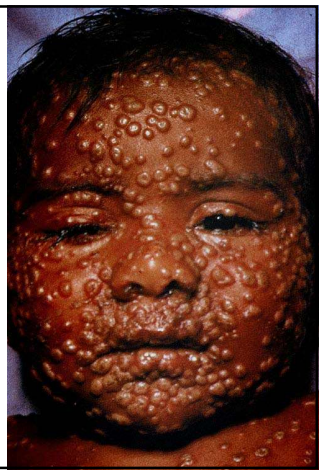

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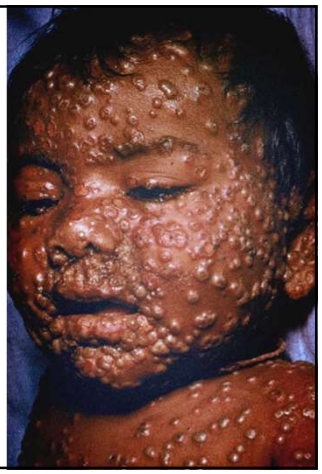

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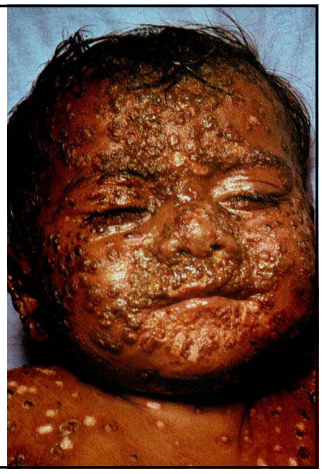
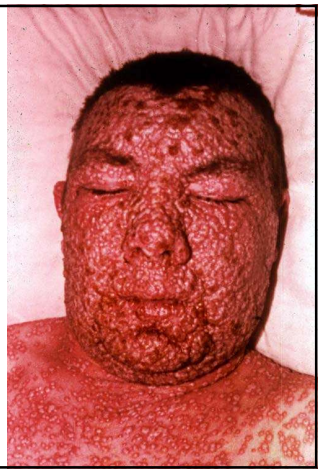


21

Confluent smallpox



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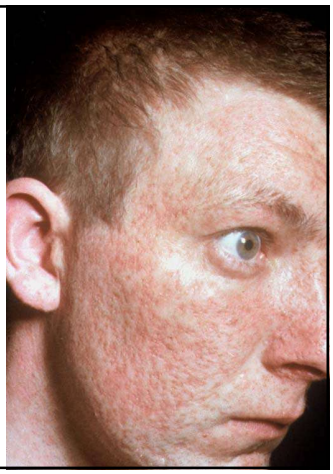
Confluent smallpox (recovered)



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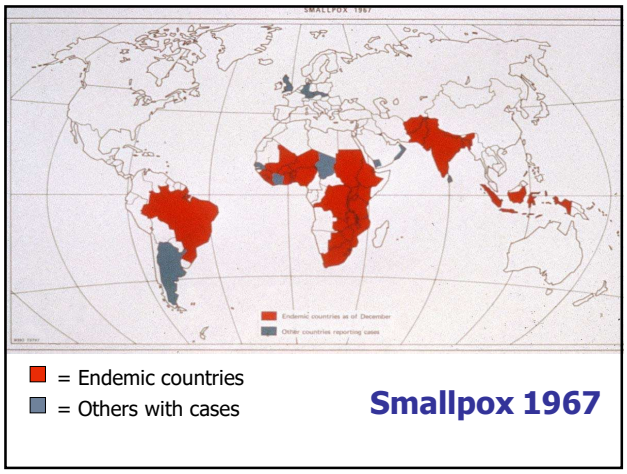

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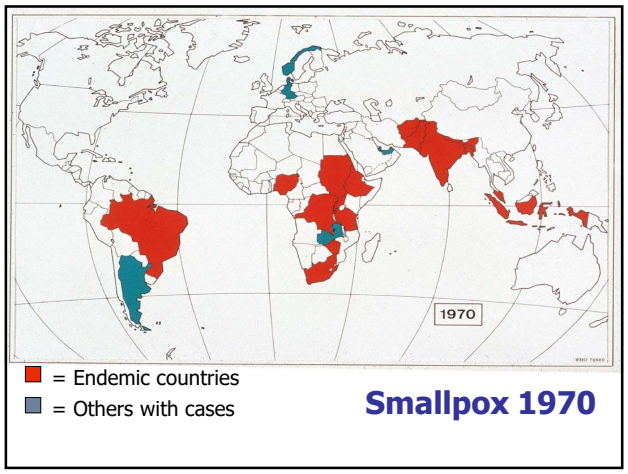

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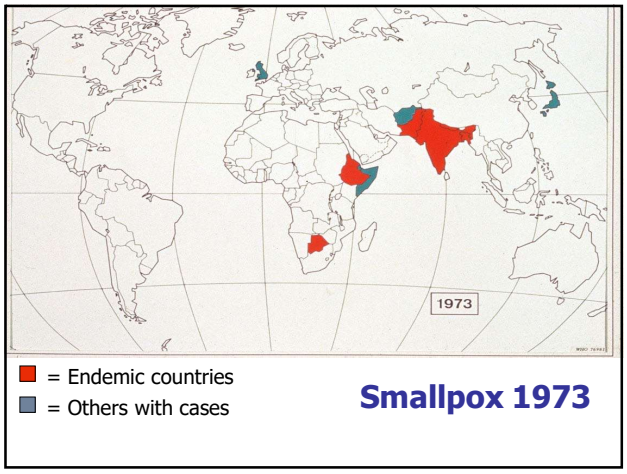

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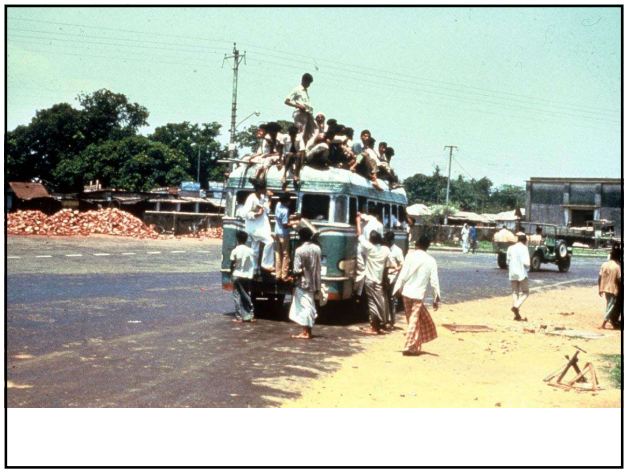

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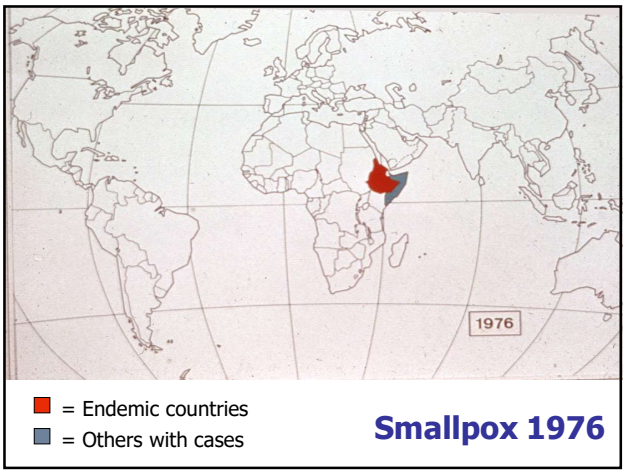

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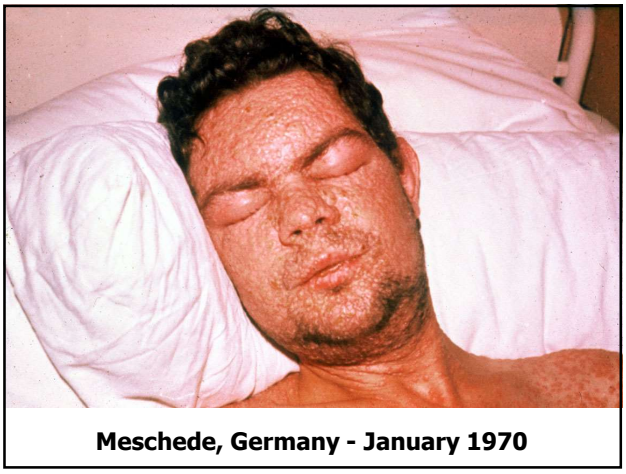

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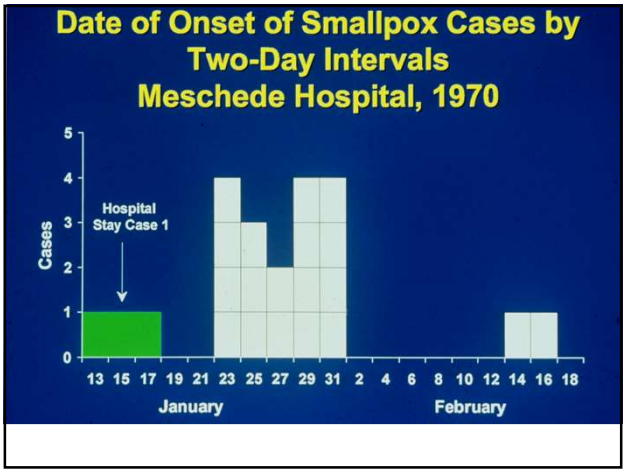

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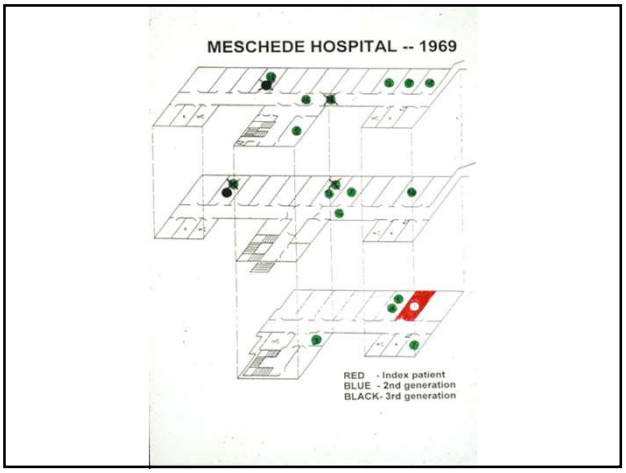

35

"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

36

Smallpox vaccine policies 1995- September 2001

- Vaccination only of workers in orthopoxvirus laboratories
- 1995 Joint DHHS-DOD Committee proposes purchase of 100 million doses
- 1999 DHHS decides to purchase 40 million doses of smallpox vaccine
  - Contract calls for delivery in 2005-06

37

Key facts about the vaccine

- Packaging
  - Container of 0.25 ml = 100 doses
- Successful vaccination with bifurcated needle = >95%
- Vaccine protects against disease if given up to 3-4 days after infection. Protection vs. death up to 5-7 days

38

Susceptibility of US Population to Smallpox -- 2004

- Vaccination stopped in 1972
- Few under 33 years of age have been vaccinated -- 40% of population
- Americans successfully vaccinated only once before 1972 may have some immunity
- Overall susceptibility – at least 75%

39

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

40

Emergency decisions

- Top priority -- procure more vaccine, bifurcated needles and VIG
  - Quantity?
  - Calf or cell culture?
  - Can vaccine be diluted?
  - Can vaccine be produced in general virology laboratories?
- Interagency committee (FDA,CDC,NIH,Army) to review progress at least every 2 weeks
- Develop strategic plans for possible outbreak

41

A Small Sampling of Problems

- With compressed schedule, problems at every stage of production process
- FDA decides
  - Existing stocks of freeze-dried vaccine must be relicensed
  - New dilution studies must be conducted
  - Bifurcated needle instruction must follow 1966 vaccine manufacturer's guide
- Interested manufacturers want "sharps standards" applied to bifurcated needles
- Pressure from many sources for mass vaccination at earliest possible time

42

U.S. Vaccine Stockpile -- 2004

	No. of doses
Wyeth DryVax	7 million
Calf-lymph - 1978	
Aventis Pasteur	85 million
Calf-lymph - 1958	
Acambis/Baxter	180 million
Vero cell - 2002	

In emergency – dilution of vaccine 1:5 is possible

43

Options for Vaccination Before an Event

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

44

A Balance of Risks

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

45

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)

46

Outbreak control

- Smallpox doesn't spread readily
- Patient transmits only after symptoms
- Most contacts are in house or hospital
  - Thus, no or few contacts at work, school, on public transportation, etc.
- Vaccine protects even when given 3-4 days after infection

47

Surveillance - Containment

a heatedly debated policy

- Isolate patient
- Vaccinate all persons who had been in a room with the patient since fever began and their household members
- Place primary contacts under surveillance with daily temperatures
  - If contact develops fever, isolate at home or special facility until diagnosed
- No compulsory vaccination; no quarantine

48

Epidemiology of Smallpox
Transmission Patterns in Europe: 1958-1973

- Outbreaks: 34
- Cases: 573
  - **Transmission in hospital: 277 (48%)**
  - **Transmission in home: 143 (25%)**
- Hemorrhagic/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**

49

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

50

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

51

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

52

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

53

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?

54

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

55

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

56

Possible uses for new vaccines

- Candidates to receive new vaccines
  - Possible immune-deficient patients/families
    ~20 million – MVA to be procured
  - Atopic dermatitis persons/families
    ~60 million
- Options for purchase of additional vaccine
  - 1 Purchase nothing more– rely on VIG
  - 2 Purchase 60 million doses LC -- $120 million
  - 3 Purchase 60 million doses MVA --1200 million

57