

Smallpox:

The Threat, the Response and New Vaccines

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Summary of presentation

- Smallpox, the disease
- The eradication program
- Vaccine and vaccination 1980 – 2006
- Where do we go from here?

"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."

Macaulay, History of England

Smallpox – Clinical Features

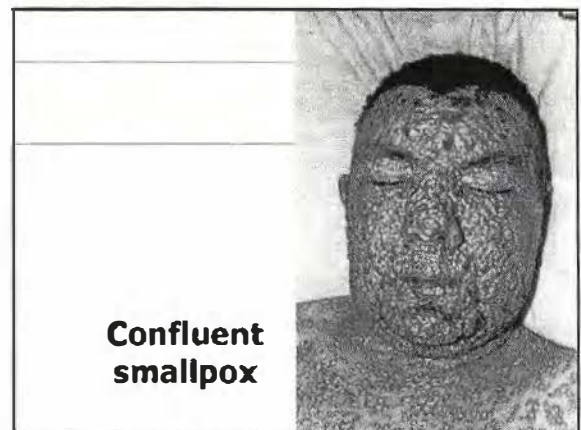
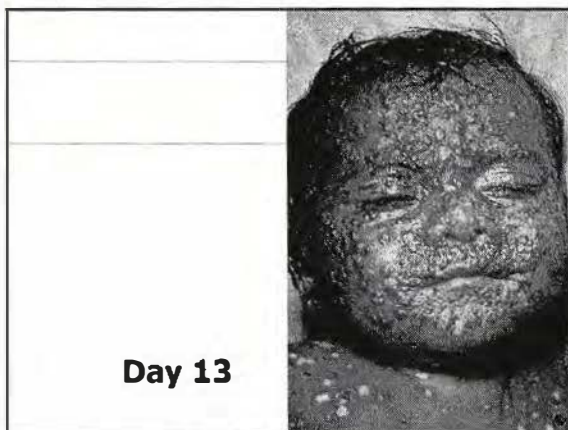
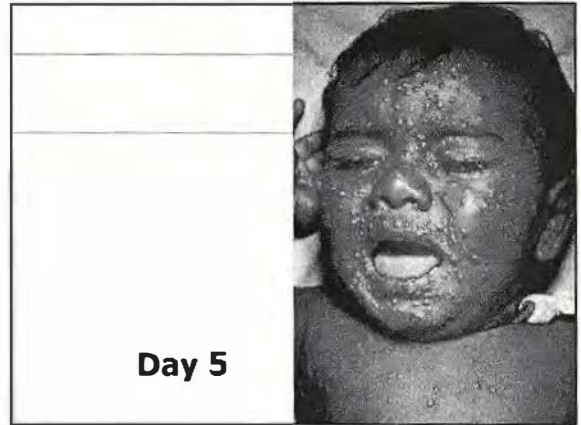
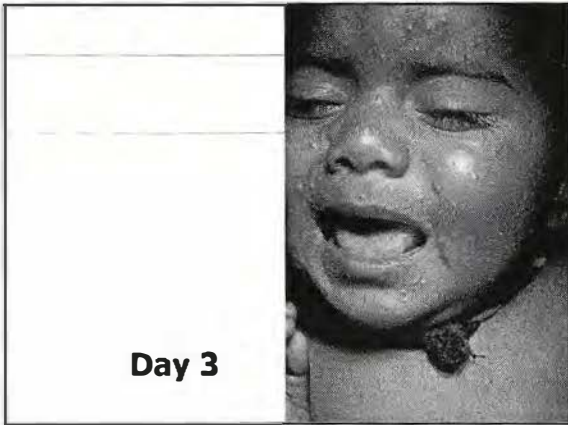
- Virus disease; man is the only host
- Incubation period – 7 to 17 days
- Severe, flu-like symptoms then rash
- No sub-clinical infections
- No anti-viral therapy available
- Case-fatality rate in unvaccinated– 30%

Day 1



Day 3





Confluent smallpox (recovered)



Landmarks in eradication

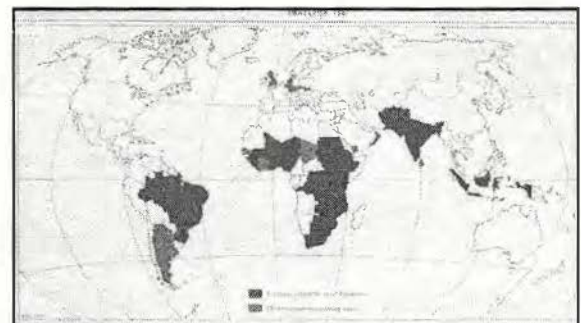
- 1959 Soviet Vice-Minister proposes eradication
 - WHO staff of 4 and little money = little progress
- 1966 U.S. and USSR propose Intensified effort
 - World Health Assembly agrees by a vote of 60-58
 - A 10 year goal is established
 - A Chief Medical Officer for smallpox is named

The Challenge

- Global status of smallpox -- 1967
 - 10,000,000 --15,000,000 cases
 - 2,000,000 deaths
 - 43 countries reported cases
- WHO smallpox program
 - Budget -- \$2.5 million
 - Headquarters -- 10 persons (5 nationalities)
 - Never more than 100 international staff

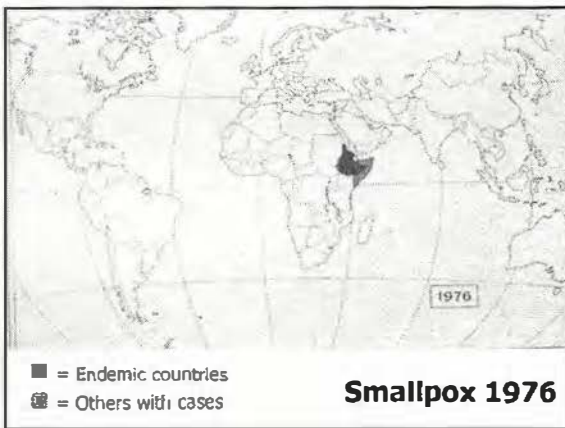
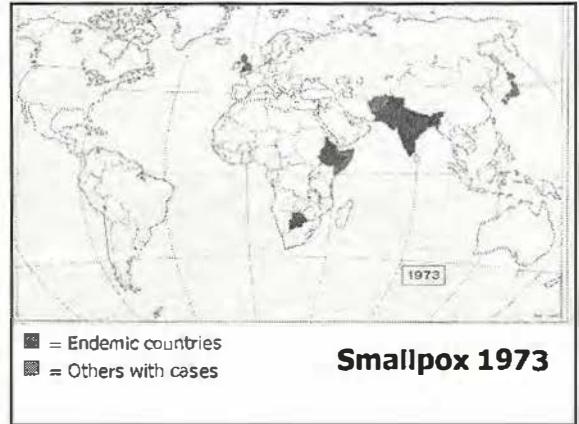
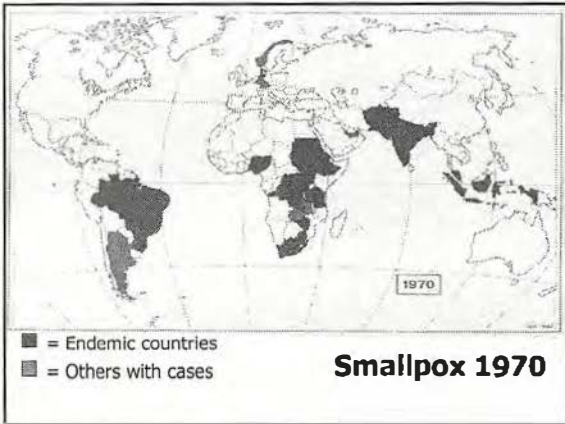
The Strategy

- Vaccination
 - Target: 80% of population
 - Freeze-dried vaccine
 - Quality control
- Surveillance-containment
 - Report every week from each health center
 - Team to investigate and do containment vaccination ("ring vaccination")

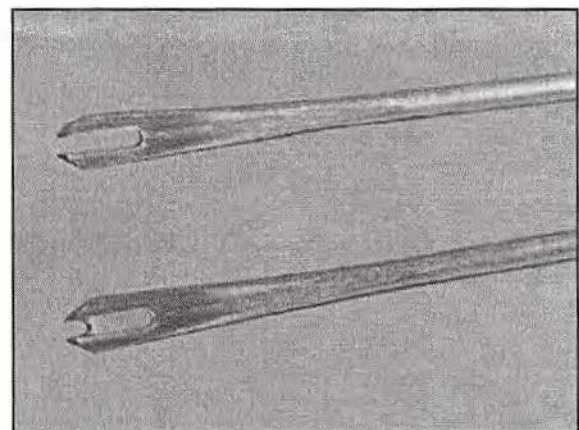


- = Endemic countries
- = Others with cases

Smallpox 1967



- Key facts about the vaccine**
- Freeze-dried – very stable
 - Packaging
 - Container of 0.25 ml = 100 doses
 - Successful vaccination with bifurcated needle >95%
 - Vaccine protects if given up to 3-4 days after infection



Post-eradication –1980+

- Eradication Declared – May 8, 1980
- Vaccination ceased by 1983
 - U.S. stopped routine vaccination ~ 1972
- Vaccine production stopped; manufacturers dismantled facilities
- WHO vaccine reserve--200 million doses
1990 WHO reserve reduced to 5 million doses

"On May 8, 1980, WHO announced that smallpox had been eradicated from the planet... Soon after ... smallpox was included in a list of ... 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."

Ajibek, 1998

Smallpox vaccine policies 1972- September 2001

- Vaccination of orthopoxvirus lab workers and military (until 1987)
- 1999 DHHS discusses purchase of 40 million vaccine doses
 - Delivery not possible until 2005-06

Susceptibility to smallpox – September 11, 2001

- 75% of U.S. population is susceptible
 - Persons under 30 years had not been vaccinated -- 45% of population
 - Persons vaccinated only once pre-1972 had little or no immunity
- World population
 - No better protected

Epidemic Response Capability September 11, 2001

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

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 research laboratories?
- Interagency committee (FDA, CDC, NIH, DoD) to review vaccine procurement every 2 weeks
- Develop strategic plans for possible outbreak

Smallpox Vaccine Reserve--2006

	No. of doses
■ Wyeth DryVax*	7 million
▪ Calf-lymph - 1978	
■ Aventis Pasteur*	85 million
▪ Calf-lymph - 1958	
■ Acambis/Baxter	170 million
▪ Vero cell - 2002	

*In emergency – dilution of vaccine 1:5 is possible

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 – low risk but potentially a catastrophic outcome without vaccine
- Frequency of adverse reactions
- Effectiveness of outbreak control

Frequency of Adverse Reactions

Expected Events (per 1960s data)

- 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

Effectiveness of Outbreak control

- Smallpox spreads slowly
- Patient transmits only after symptoms
- Most contacts are in home or hospital
 - Few or none at work, school, etc
- Vaccine protects even when given 3-4 days after infection

Epidemiology of Smallpox

Transmission Patterns in Europe: 1958-1973

- Outbreaks: 34
- Cases: 573
 - Transmission in hospital: 277 (48%)
 - Transmission in home: 143 (25%)
- Hemorrhagic cases – a threat to hospitals
 - Bradford, UK (1961) 10 cases
 - Germany (1970) 16 cases
 - Yugoslavia (1972) 38 cases

Surveillance - Containment

- Isolate patient
- Vaccinate all who have been with patient since fever and their household members
- Contacts placed under surveillance with daily temperatures
- If contact develops fever, isolate
- No compulsory vaccination; no quarantine

Vaccination policy

tumultuous debate thro 2002

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

The Vaccination Program closes

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

Smallpox vaccine complications

Military Experience *

- Total screened 757,000
- Total vaccinated 708,500 (94%)
 - Post-vaccinal encephalitis - 1
 - Progressive vaccinia - 0
 - Eczema vaccinatum - 0
- Infection in contacts - 29
- Doses of VIG used - 3

*See Poland GA, Grabenstein JD, Neff JM (2005) Vaccine 23:2078-2081

Smallpox vaccine complications

Civilian Experience *

- Vaccinated –38,440
 - Cutaneous complications

	Reported	Actual
Prog. Vaccinia	7	0
Eczema vaccinatum	3	0
General. Vaccinia	29	2
 - Cardiac complications – no more than expected normally

Smallpox vaccine

Cardiac complications -- military

- Myopericarditis 86
 - Primary vaccinees 16/100,000
 - Onset 2 to 25 days
 - Fever, chest pain, EKG changes, enzymes
 - Full recovery (except 2, still uncertain)
- Dilated cardiomyopathy 4
- Ischemic events – no more than would be expected in a comparable population

Alternative vaccines--MVA

- MVA (Modified Vaccinia Ankara)
 - Non-replicating vaccine derived by multiple passages in cell culture (CEF)
 - Developed in Germany in 1960's
 - Good protection as measured by antibody and challenge studies
 - Phase 2 studies in progress
 - RFP issued by DHHS for purchase of enough to vaccinate 10 to 60 million persons

Alternative vaccines – LC16m8

- Greatly attenuated, replicating vaccinia strain derived by multiple passages in cell culture (fetal rabbit kidney)
- Developed in Japan in 1970s
- Licensed in Japan and 50,000 children vaccinated
- Good protection as measured by antibody and challenge studies
- Phase 2 studies in progress

Future utilization of smallpox vaccine

- Major review is being completed
- Questions posed
 - Do we expect to ever have routine community-wide vaccination programs?
 - How can we know that a new vaccine or drug would protect against smallpox?
 - How many would need to be vaccinated to demonstrate that a new product is safer than the existing replicating vaccine?

Future utilization of smallpox vaccine

- Cost implications of a new product
 - New product development -- \$800 million
 - Purchase of 100 million doses
\$1 billion dollars plus
 - Replenishment of expiring stocks of product
 - Annual payments for continuing production to retain a "warm base" for emergency need
- Present stocks include sufficient highly stable vaccine to vaccinate the population and sufficient VIG for treatment of complications

- Despite having a vaccine that is 200+ years old; a disease that has been eradicated; and 5 years of intensive post 9/11 study and debate, there are now more questions than ever.

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