

- Vaccine 1796
 - Why 180 years to get rid of the disease
 + Vaccine was the key

Smallpox vaccine...

sine qua non for eradication

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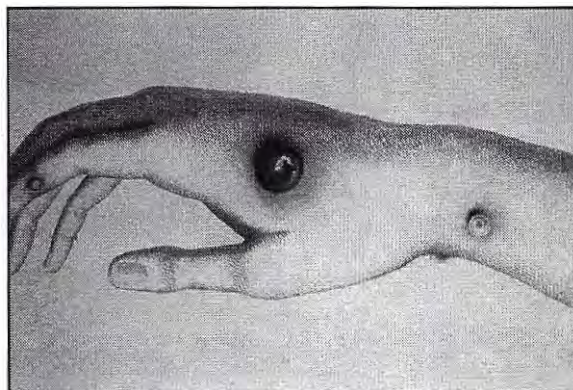
FDA Countermeasure Lecture Series
 13 February 2012

Summary of presentation

- Jenner and the world's first vaccine -- 1796
- Smallpox, the disease
- Vaccine development -- 150 years required
- The eradication campaign -- highlights
- An emerging bioweapons threat -- 1995-2001
- Emergency vaccine production -- 2002



Edward Jenner



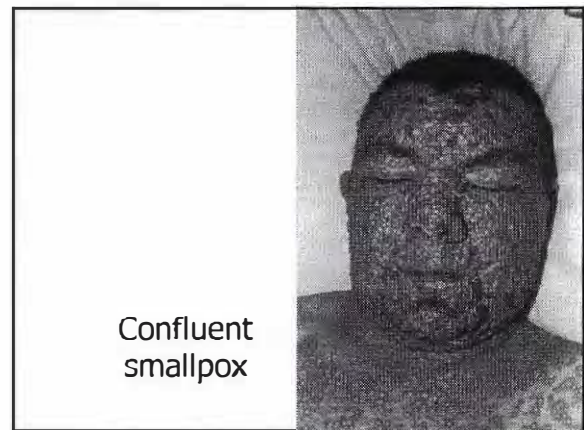
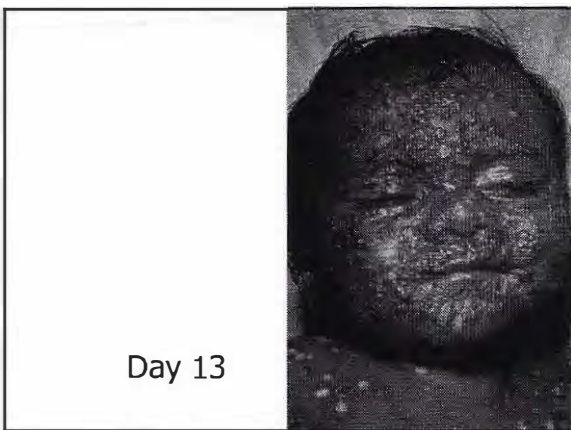
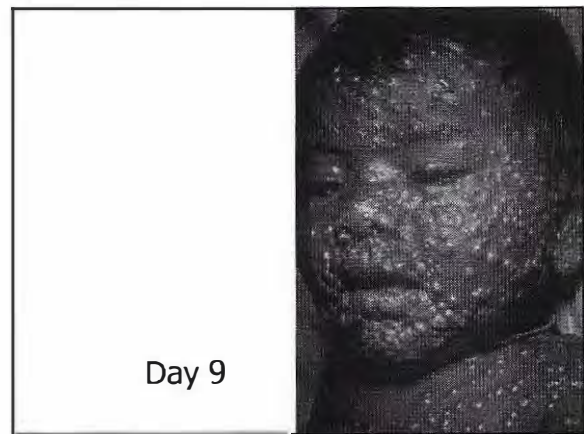
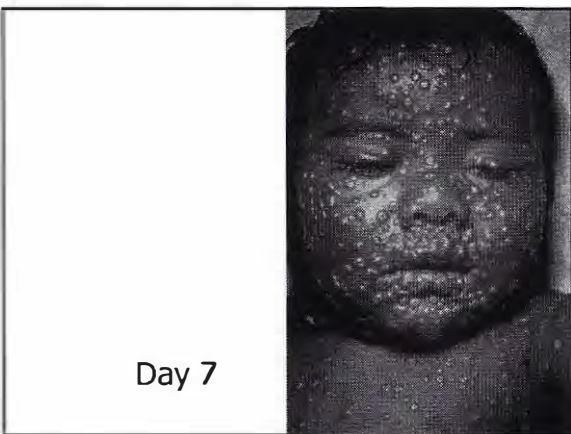
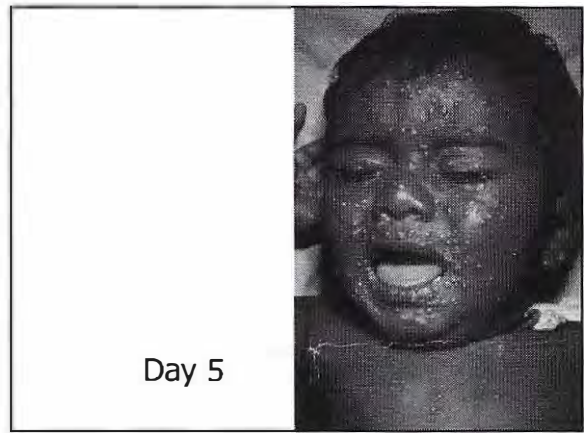
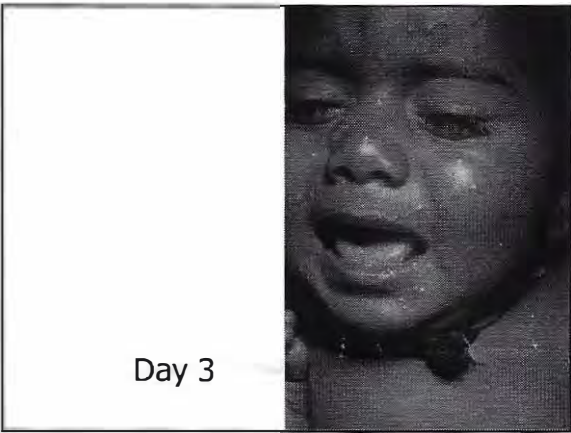
Cowpox on the hand of Sarah Nelmes

"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."

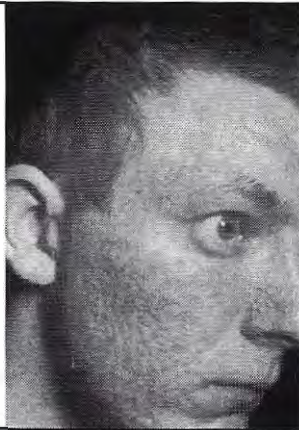
Macauley, History of England

Smallpox – Clinical Features

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



Confluent
smallpox
(recovered)



Smallpox in history

- Ramses V and three other mummies show evidence of death from smallpox 3500+ yrs ago
- Smallpox gods in Asia and Africa
- Massive numbers of deaths in Amerindians changed the course of European settlement
- Abraham Lincoln and the Gettysburg address

Smallpox in the 20th century

- Deaths – 300,000,000 before 1978
NYTimes: 120,000,000 died directly or indirectly as a result of armed conflict
- Compulsory vaccination in the U.S. until 1972
Last case in U.S. – 1949
- International travelers carried a "yellow booklet" documenting vaccination in past 3 years

Vaccine Development

A short history 1796-2001

Arm to arm vaccination 1796 to 1880s

- Source: vaccinia pustule
- Sometimes contaminated with syphilis

Vaccine grown on animal skin – 1870s to 2001

- Animals: calves, sheep, water buffalo
- Scarification of shaved skin
- Growth of vaccinia for 6 to 9 days
- Sacrifice animal, scrape off pustules, purify
- Add glycerol and phenol (bactericidal)



Key elements for eradication

a better vaccine and vaccination method

Heat stable vaccine

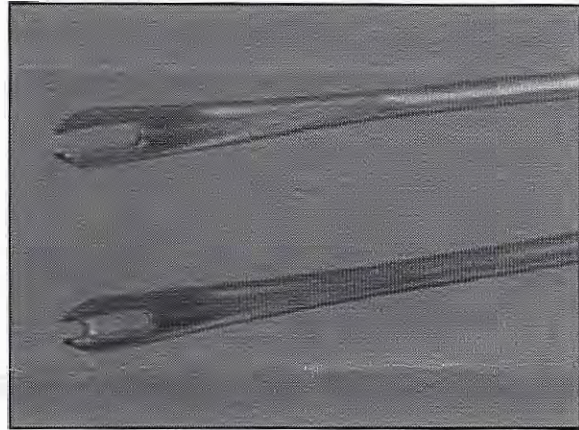
- Process for commercial freeze drying -- 1953

Potency and purity standards

- WHO Committees -- 1958
- Production manual -- WHO consultations -- 1968
- Testing laboratories -- Netherlands, Canada -- 1969

The bifurcated needle

- Invented by Ben Rubin -- 1964



The birth of the WHO global program

Director General submits a plan to World Health Assembly -- May 1966
10 year program -- WHO budget of \$ 2.4 million/year

Objections by delegates

- Not feasible
- Demand that WHO budget not be further increased

Voting -- 58 votes needed; 60 voted in favor

The Challenge

- A director is chosen
- Status of smallpox -- 1967
 - >10,000,000 cases
 - 2,000,000 deaths
 - 43 countries reported cases
- Program staff
 - Headquarters -- 6 professional and 3 secretaries
 - International staff -- never more than 150

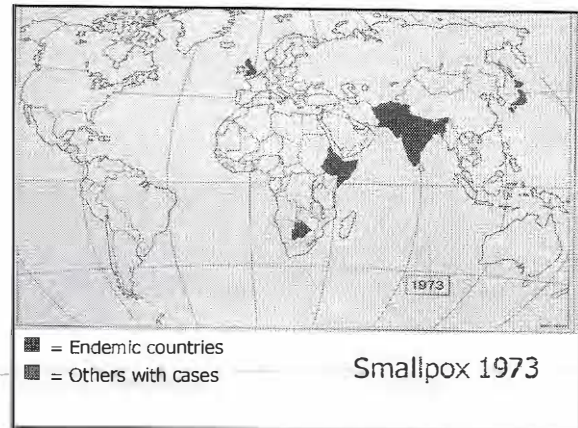
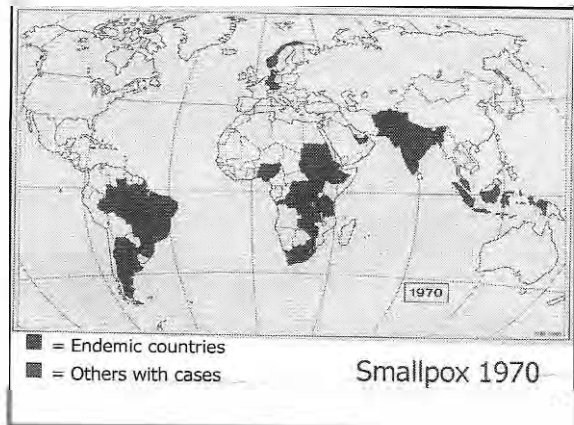
The strategy

- Vaccination of 80% to minimize spread
- Surveillance
 - To obtain a weekly report from every health center and hospital
- Containment
 - "Fire-fighting teams"
 - Investigate every case
 - Contain outbreaks with ring-vaccination



- = Endemic countries
- = Others with cases

Smallpox 1967



A new strategy – June 1973

Search every village in India in 10 days
120,000 health staff
Containment teams to go to every outbreak
By the third round, every house was being visited

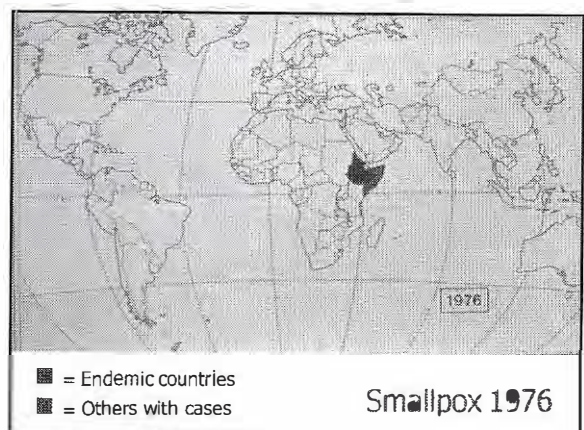
Catastrophic problems Jan to May 1974

- Gasoline crisis
- Railroads, airlines, finally health workers on strike
- Worst floods in three decades
- India detonates an atomic weapon—May 1974

Indian Independence Day
August 15, 1975

Prime Minister Indira Gandhi

- Salutes India on its 28th Anniversary
- Announces India's freedom from smallpox for the first time in written history





Ali Maalin - 26 October 1977

Eradication is certified by World Health Assembly -- May 1980

- By 1983 vaccination ceased
 - U.S. stopped routine vaccination -- 1972
- Manufacturers dismantled facilities
- Vaccine reserves in 1998
 - WHO -- 5 million doses
 - Total for all other countries-- ?90 million doses

The Threat of Biological Weapons

- Biological Weapons Convention--1972
 - Cessation of research on offensive weapons
 - Destruction of existing stocks
- 1992 USSR Bioweaponer Alibek defects
 - USSR program: 50 laboratories; 60,000 staff
 - Preferred agents: smallpox, anthrax
 - Smallpox production capacity -- 20+ tons per year
 - USSR laboratory research staff disperse

Policies re: smallpox vaccine

1972- September 2001

- Vaccination only of orthopoxvirus lab workers
1999 -- HHS decides to purchase 40 million vaccine doses because of threat
- Delivery not possible until 2006+
 - Decision still pending by 2001 attack

A new reality

September 11, 2001

Meeting with Secretary Thompson-- Sept. 16

- Possible second attack--smallpox or anthrax
- Status of country
 - None <30 years of age have ever been vaccinated
 - 75% of population susceptible
- Vaccine availability
 - 15 million doses in storage
 - No vaccine manufacturer in the world

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, needles

- Quantity?
- Calf or cell culture?
- Can vaccine be diluted?
- Can vaccine be produced in research laboratories?

Interagency committee

FDA, CDC, NIH, Army, et al to review vaccine procurement progress every 2 weeks

Emergency actions -- post 9/11

- Vaccine – 300+ million doses ready in 18 months to be used only in emergency
Vaccine produced in tissue culture with Dryvax clone
- Emergency Use Authorization legislation
Balance of risk of use vs. seriousness of threat
- Diagnostic labs increased from 2 to >100
- Health departments given \$1 billion for response
- Plan for strategic utilization of vaccine

On-going agenda for possible new MCMs

Goals -- as stated by U.S. delegates at the World Health Assembly

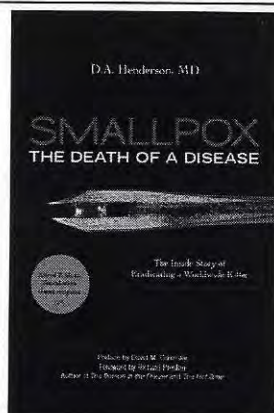
- A vaccine equivalent to existing ACAM2000 strain (presumably in efficacy and heat stability) but which has no adverse effects (MVA; LC16m8)
- Two anti-viral products which have different modes of action, for use in treatment of cases (ST-246, cidofovir derivative)

Contrast: February 2012 and September 2001

Thanks to heroic efforts by ASPR, FDA, CDC, and NIH, we have supplies of a highly effective, inexpensive, heat-stable vaccine adequate to cope with the most serious of the bioterrorist threats to the U.S.

We hope and expect that the vaccine will never be used.

How much more should be spent on smallpox countermeasures?



Strategy for epidemic control

Targeted vaccination

- Cases and case contacts
- Hospital personnel, first responders
- Limited area-wide vaccination

Rationale

- Smallpox spreads slowly
- Patient transmits only after symptoms
- Most contacts are in home or hospital
- Few or none are at work, school, etc

Frequency of Adverse Reactions

Expected Events (per 1963-68 data)

Life-threatening complications (per million vaccinees)

- Post-vaccinal encephalitis (3)
- Progressive vaccinia (1)
- Eczema vaccinatum (12)

Less serious

- Generalized vaccinia, rash, fever
- Accidental inoculation

Myopericarditis