

SARS / pandemic flu / possible agents

Smallpox is the best, the world's most feared disease - the plague, cholera. Problems we will need to confront repeatedly in the future.
3500 years to a cure
cannot forget it as I will this year.

NOT WEBB
PUT TOGETHER

Problems we will need to confront repeatedly in the future.

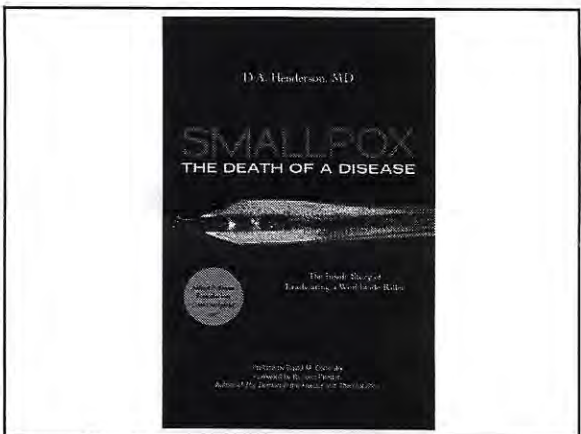
End of the World's Greatest Pestilence

...but some continuing concerns

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July, 2013



SARS generated enormous interest in medical/public health/communities for pandemic and responses for serious exotic diseases - Earthquakes, floods, emergency infectious like flu and AIDS. Travel, increasing population worldwide more.

One of the potentially most serious - Smallpox
Eradicated now but threat of bioterrorism

"There has been no greater medical - or humanitarian - miracle in modern times than the eradication of smallpox... (It is the saga of a) day-to-day struggle for international cooperation in a divided world; it offers a winning blue print for the great medical challenges to come."

David Oshinsky - Winner of the 2006 Pulitzer Prize in History

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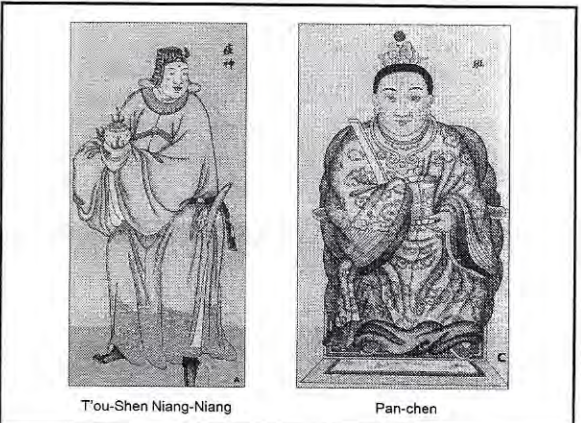
Smallpox - a unique historic disease

- Severe febrile disease with death rate of 30%
- Transmission by face-to-face contact
- Man was the only host
- Patient has permanent immunity on recovery
- A heat-stable vaccine protects with one dose

Center for Biosecurity

Smallpox in history

- All countries experienced smallpox, transmission was possible in any climate
- Most serious of all the pestilential diseases
- Ramses V and three other mummies died of smallpox 3500+ years ago
- Smallpox gods in Asia and Africa



Smallpox in the 20th century

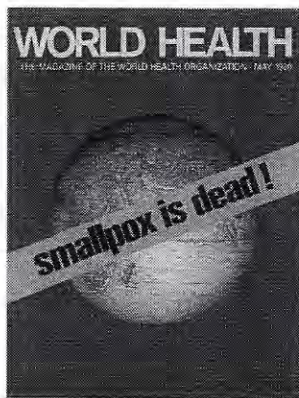
- Deaths – 300,000,000 died of smallpox
- NYTimes: 120,000,000 died directly or indirectly as a result of armed conflict
- Last cases of smallpox
 - United States – 1949
 - China Taipei – 1954
 - China – 1961
 - (variolation cases until 1965)
- Compulsory vaccination in the U.S. until 1972

World Health Assembly

May 8, 1980

Eradication program, begun in 1967, concludes

- The World Health Assembly declares solemnly that the world and all its peoples have won freedom from smallpox
- Smallpox vaccination should be discontinued in every country



Post-eradication

1980-2003

- Vaccine production stopped in 1980; manufacturers dismantled facilities
- Vaccination stopped world wide – 1982
- Smallpox virus kept in 2 labs (U.S., Russia)
- WHO vaccine reserves <30 million doses

Smallpox as a biological weapon

- 1972 Biological weapons convention
 - Signed by all countries but no verification
- 1989-92 Suspicion about Soviet BW program
- 1992 Soviet BW program is confirmed

A defector provides details -- 1992

- Deputy Director of USSR bioweapons program
 - 60 laboratories with 50,000 staff
 - Priorities – smallpox, anthrax, plague
- USSR dissolves – 1992-1993
 - Laboratory staffs cut by half or more
 - Many scientists leave the USSR for Europe, U.S., other countries

BW threat— medical view until 1998

- Biological weapons are morally repugnant
 - Limited teaching or research about diseases of principal concern in medical schools
 - No staff or program at CDC, NIH
- A turning point— IDSA Infectious Disease Seminar—September 1997
 - Multiple hospitals organize Grand Rounds
 - Hopkins Center for Biosecurity created (1998)

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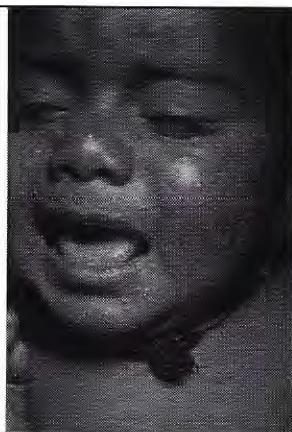
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Sept. 11, 2001 and a changed world

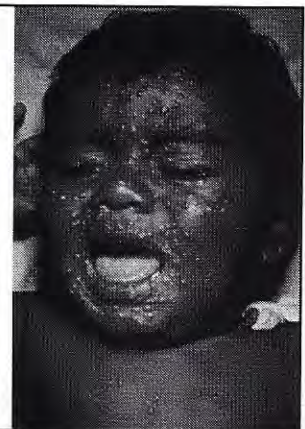
- Sunday, September 16 – an evening meeting
- Intelligence intercepts – a second attack
- Decision to create an Office of Emergency Preparedness with Asst. Secretary as director
- The first of 22 anthrax cases becomes known two weeks later

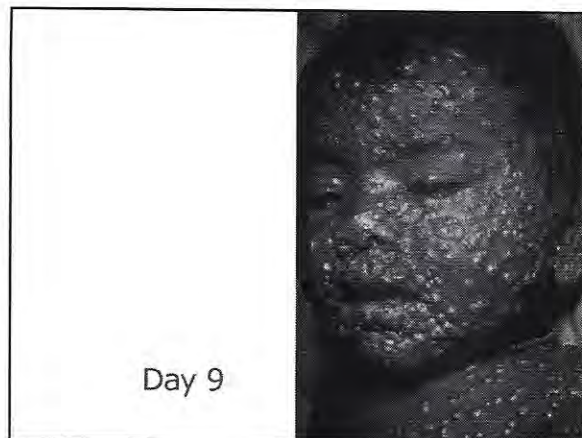
The Disease

Day 3

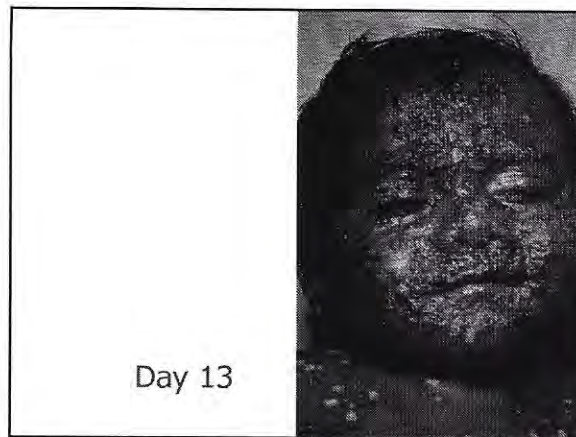


Day 5

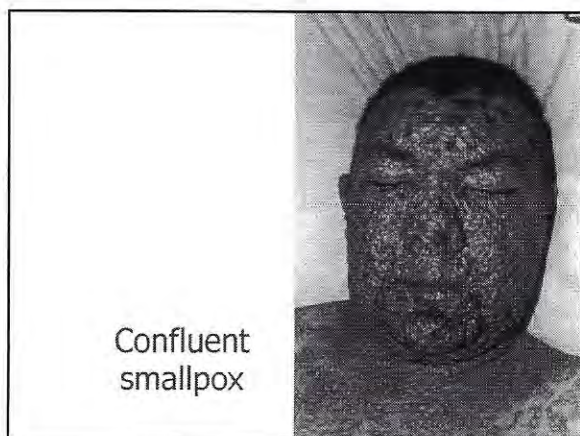




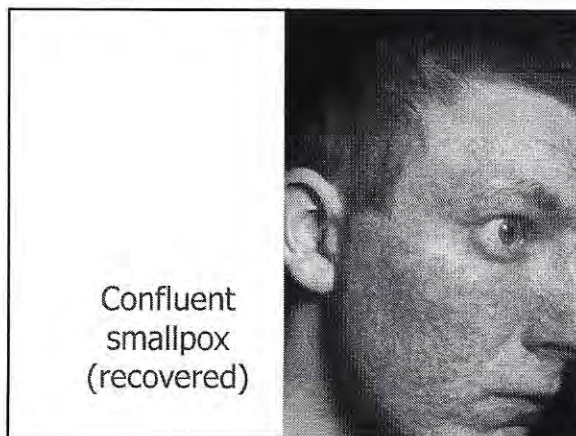
Day 9



Day 13



Confluent
smallpox



Confluent
smallpox
(recovered)

WHO Smallpox eradication program ...a brief reprise

Assembly requires DG to submit a plan --1966

- Strategy
 - Systematic mass vaccination to reach 80%
 - Surveillance and containment
- 10 year program – WHO budget of \$ 2.4 million/year
- Objections by delegates
 - Not feasible
 - Demand for no further increases in WHO budget
- 58 votes for acceptance; 60 voted for approval

Surveillance-containment strategy

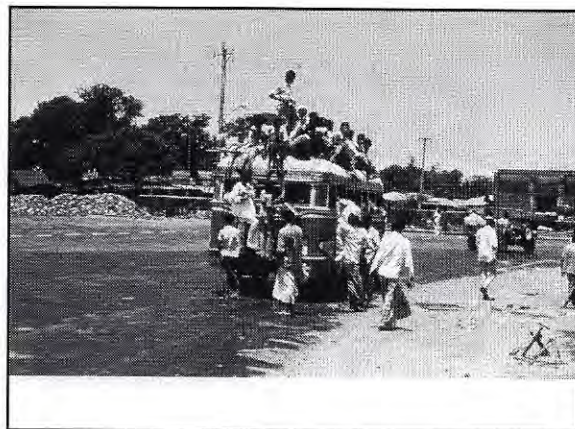
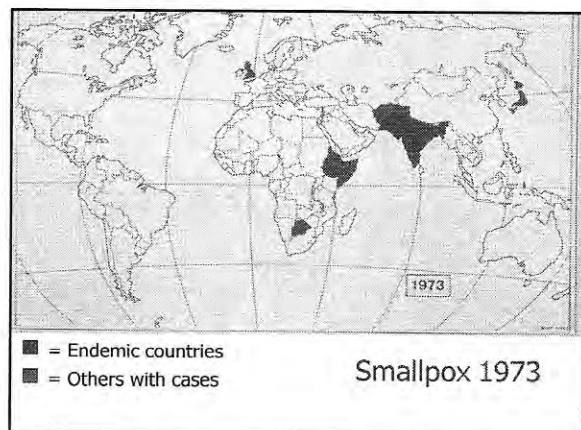
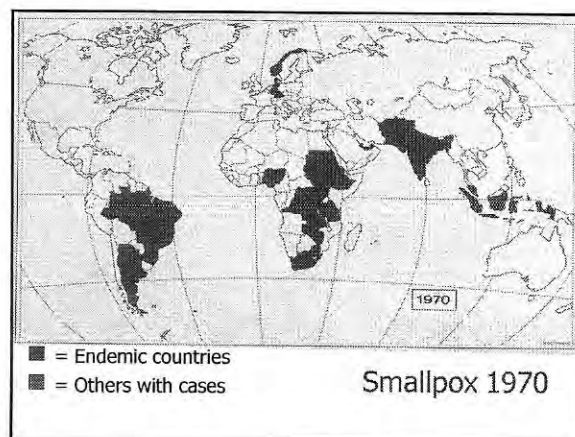
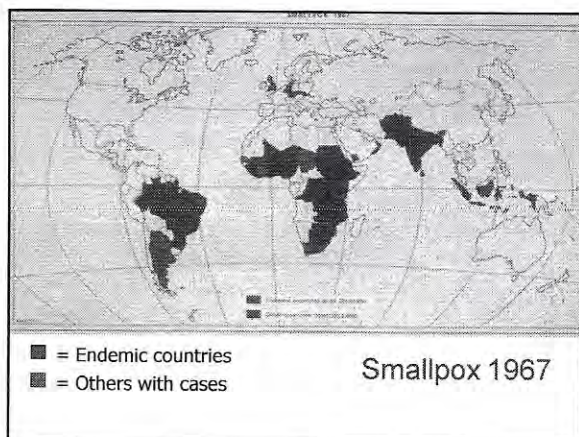
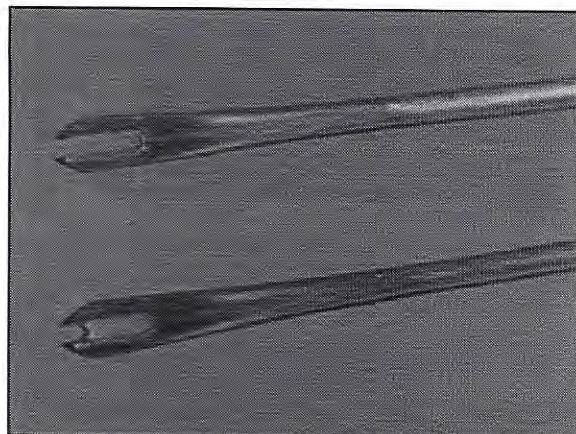
- Operational plan
 - Surveillance – weekly report from all health units
 - Teams – to investigate and contain outbreaks
 - Epidemiological research on smallpox
 - The textbooks prove to be wrong
 - "Smallpox spreads like a prairie fire"
 - "Revaccination is needed every 3 to 5 years"

Vaccination methods

- Research to find faster, better methods
 - Bifurcated needle—multiple puncture method
 - One-fourth as much vaccine required
 - Training time -- 15 minutes
 - Reusable after sterilization
 - Cost -- \$5 per thousand
- Target for coverage -- 80%
 - Evaluation teams

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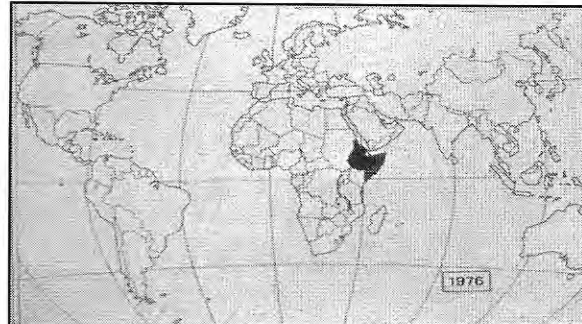
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India -- the pivotal challenge

1973-75

- India -- the "home of smallpox"?
 - Population -- 550,000,000
 - Surveillance-containment strategy--not working
 - June 1973 -- search every village> every house
 - 130,000 health staff in 10 days
 - Results of first search -- October
 - Spring 1974 -- the darkest days
 - Gas crisis + strikes by airlines, railway, floods
 - India explodes a nuclear device



■ = Endemic countries
■ = Others with cases

Smallpox 1976

The last strongholds

Ethiopia and Somalia

- Ethiopia -- three times the size of Taiwan
 - Largely highland --over 5000 feet
 - Health facilities serve 5% of 30 million people
 - Travel largely by donkey and on foot
 - Emperor is assassinated; Marxist take-over
 - No foreign staff outside of Addis except smallpox teams
- Civil war, floods, famine, kidnapping, hostages
- Somalia -- the final chapter



Ali Maalin - 26 October, 1977

Sept. 11, 2001 and a changed world

- Sunday, September 16 -- an evening meeting
- Intelligence intercepts --a second attack
- Decision: to create an Office of Public Health Emergency Preparedness with Asst. Secretary
- Congress provides emergency appropriation of \$3 billion

The threat of a smallpox virus release

- 75% of U.S. population was susceptible
 - Persons under 30 years --not vaccinated
 - 45% of population
 - Vaccinees pre-1972-- little or no immunity
- World population
 - No better protected

Emergency decisions

- Top priority -- procure more vaccine
 - Quantity -- 40 million doses
 - New production method necessary
 - Can vaccine be produced in general virology laboratories? No
- Final decision: obtain 300 million doses
- Anticipated 5 year effort completed in 18 months
- Vaccine shelf life at -20°C: indefinite

Strategy for smallpox vaccine use a balance of risks

Probability that smallpox would be used as a weapon: considered to be less likely than use of any number of other possible microbes

Frequency of vaccine adverse reactions: entirely acceptable if confronting an imminent threat. (Some pox virologists have a different view).

Effectiveness of outbreak control

- Smallpox spreads slowly
- Patient transmits only after rash appears
- Isolation of contacts is very effective
- Most contact spread is in home or hospital
 - Few or none are infected at work or school
- Vaccine protects even when given 3-4 days after infection

Two established smallpox vaccines

- LC16m8 – licensed and produced in Japan
 - Live, attenuated, derived from Lister strain
 - Single dose scarification
 - Evaluation in >100,000 children
 - ACAM200 – licensed, to be produced in U.S.
 - Live, attenuated, derived from NYC8H (U.S) strain
 - Single dose scarification
 - Evaluation in several million vaccinees
- Note: LC16m8 has fewer secondary reactions but is not quite as antigenic as ACAM 2000. Cost ~\$3.00/dose*

A new experimental vaccine

- Imvamune (MVA, i.e. Modified Vaccinia Ankara) – produced by Bavarian-Nordic, Germany
 - Inactivated, attenuated, from Turkish vaccine strain and several hundred passages in eggs.
 - Two subcutaneous injections 4 weeks apart
 - Safety evaluation in < 10,000 persons
 - Not licensed

*Note: need for two injections makes this impractical for epidemic use.
Cost ~\$US 40/two injection dose*

A new anti-viral agent

- Arestvyr (ST 246) – produced by Siga
 - Antiviral agent effective in prevention and treatment of poxvirus in some animal studies
 - Treatment course is 10 days
 - No evident toxic effects in humans

Note: Pathophysiology of human smallpox suggests drug would not be effective if given after rash develops. Drug cost (~\$US 130 per course) precludes widespread use in prevention

Summary

■ Smallpox virus: status today

Restricted to 2 laboratories (U.S. and Russia)

Research continues for a new vaccine which protects with one dose and has no adverse reactions and for an anti-viral drug to treat the disease if it occurs

All protocols cleared by international committee

Laboratories regularly inspected for safety

In brief, smallpox seems to be safely locked up within several committees. Being talked to death.

Smallpox today

- Known smallpox virus stocks reside in only 2 laboratories under high biological security
- Destruction of these remaining stocks to be discussed in 2014 World Health Assembly
- The question of an enlarged WHO stockpile of smallpox vaccine is under discussion

A hopeful future

- From *Smallpox: death of a Disease*:

"We are only beginning to realize the potential of public health... It is a field begging for fresh, resourceful ideas and a new generation of professionals who are not constrained by 'knowing' what can't be done. So it was with so many who contributed so much to making smallpox eradication a possibility."

