

1980 - closed chapter -
(no marketable skills)

EDONBURGH

6-21

Queen

Smallpox Vaccines

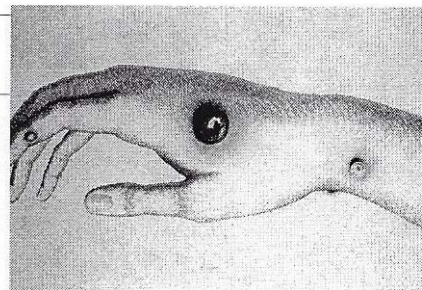
D. A. Henderson, MD, MPH
Society for General Microbiology
Edinburgh, Scotland
7 April 2003

"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



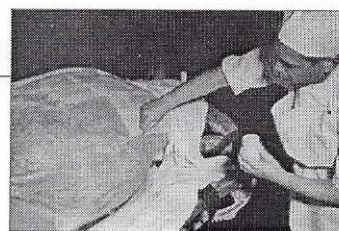
Edward Jenner



Cowpox on the hand of Sarah Nelmes

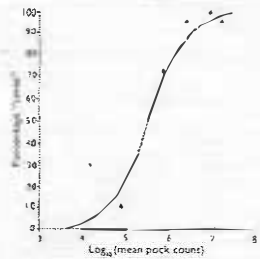
Smallpox vaccine--landmarks

- 1798 - Cowpox, the first vaccine
- Until late 1800s - arm-to-arm spread
- Late 1800s to 1980 - Usually grown on calves, sheep, water buffalo
 - Two principal strains
 - New York City Board of Health
 - Lister Institute strain

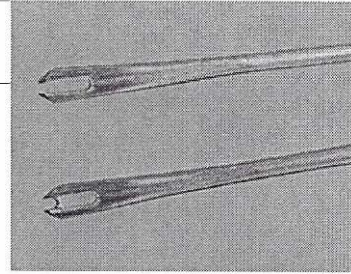


Vaccine collection from cows seeded with vaccinia

Vaccine Titer and Primary Takes



Cockburn, 1969



Bifurcated Needles

U.S. Smallpox Vaccines

	No. of doses
■ Wyeth DryVax	15 million
■ Manufactured 1978-9	
■ Aventis Pasteur	85 million
■ Manufactured ca. 1958	
■ Acambis /Baxter	209 million
■ Manufactured 2002	

Wyeth DryVax

15 million

- NYCBH strain, calf skin, lyophilized
- Licensed product
- Take rate in unvaccinated adults
 - Undiluted 97% (103/106)
 - 1:5 99% (232/234)
 - 1:10 97% (335/340)
- 100 dose vials

Aventis Pasteur - "Wetvax" 85 million

- NYCBH, calf skin, wet frozen, glycerol
- IND status -- emergency use only
- Diluted 5:1 -- 500 dose vials

ACAM 2000

209 million

- Acambis/Baxter
- NYCBH-derived strain -- Vero cells
- Lyophilized, 100 dose vials
- In Phase II trials
- Licensure -- early 2004

Intravenous Vaccine Immune Globulin

- Derived from plasma from plasma from paid revaccinated donors
- Quantity available – enough to treat serious reactions among 40 million vaccinees
- By June, sufficient to deal with complications if 300 million vaccinees

MVA – Next Generation Vaccine?

- Non-replicating attenuated vaccinia strain (Modified Vaccinia Ankara) originally developed in Germany
- Vaccination by IM –either 2 doses or 1 dose followed by Dryvax
- Contract awarded for development and initial manufacturing of MVA
- Initial phase I trials have begun

Lc16m8 – Next Generation Vaccine?

- Temperature-sensitive clone of the Lister strain developed in Japan in the 1970s
- Trials to begin soon in US and Japan
- Grown in primary rabbit kidney
- Tested in 50,000 Japanese children – less skin reaction and fewer systemic symptoms; apparently similar serological responses to Lister strain

Options for Vaccination Before an Event

- ~~Vaccinate no one~~
- **Vaccinate those at highest risk, candidates:**
 - Healthcare workers
 - First responders
 - Postal workers
 - Other essential personnel
- **Vaccinate anyone desiring to be vaccinated**
 - Recommend vaccination
 - Recommend against vaccination
- ~~Make vaccination compulsory~~

Smallpox Vaccine Expected Adverse Events

- **Life-threatening complications No/million**

■ Post-vaccination encephalitis	2-3
■ Progressive vaccinia	1-2
■ Eczema vaccinatum	10-15
- **Less serious**
 - Rash, fever, accidental inoculation
 - Pericarditis and myocarditis (NEW)
- If 100 million vaccinated – 100-400 deaths and 1500 to 2000 complications perhaps requiring hospitalization

CI Vaccinia experience --2003

- Military vaccinations – 325,000+
 - Contraindicated -self or family 25%
 - Sick leave (average –1.5 days)
 - Hospital 3% Theater 0.5%
 - Vaccine transfer to others
 - Spouse (4); close contacts (5); patients (0)

II Vaccinia experience –2003

- Military
 - Generalized vaccinia - 17 (all mild)
 - Encephalitis - 2 (recovered)
 - Progressive vaccinia - 0
 - Eczema vaccinatum - 0
 - Myocarditis - 11 (recovered)

III Vaccinia Experience - 2003

- Civilian -- 24,000 vaccinated
 - Myocarditis 2
 - Angina association 2
 - Myocardial infarction 3 (2 deaths)

Temporal or causal

A Balance of Risks

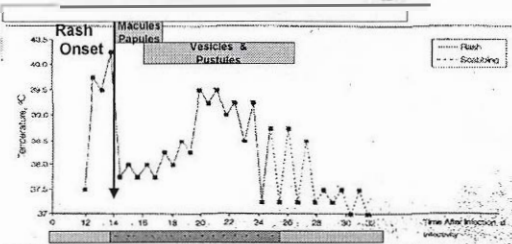
- What is the likelihood that smallpox will be used as a weapon?
- What will be the frequency of adverse reactions in 2003 and what will be the public acceptance?
- How rapidly could an epidemic be controlled?

The Spread of Infection

Spread of smallpox is comparatively slow

- Household spread -secondary household attack rates
 - Measles 76%
 - Chickenpox 74%
 - Smallpox 58%
- Community spread
 - Measles and chickenpox -- spread more rapidly than smallpox because of transmission before symptoms

Clinical Course of Smallpox



JAMA, June 9, 1999; Vol 281, No. 22: 2129

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
- Seasonal variation
 - Dec to May 24 importations average= +45.6 cases
 - June to Nov 10 importations average= + 0.5 cases

Surveillance

- First persons to detect cases – ER staff
 - Prodromal smallpox illness is usually severe and incapacitating
- Call on 24/7 line to health department
 - Contact of other regional facilities
- Emergency transport of specimens to CDC and lab network

Containment

- Isolate patient in room/ward under negative pressure
- Vaccinate all persons who had been in a room with the patient since he became febrile (primary contacts)
- Place primary contacts under surveillance with twice daily temperatures
 - If a primary contact develops fever isolate at home or in special facility until diagnosed
- Vaccinate all household contacts of primary contacts (secondary contacts)

Other Steps/Principles

- Make vaccine available on request to those in the general geographic area
- Prompt, current, accurate communication to public
- Not generally desirable:
 - Compulsory vaccination
 - Quarantine of city or groups of people
 - Closure of airports, suspension of transport

Preparatory steps in progress

- Vaccine –
 - **Stockpiled**--available anywhere in 12 hours
- Plan in each region to make vaccination widely available in 7-10 days
- Plan in each region to accommodate 500 patients in negative pressure rooms
- All ERs to have negative pressure rooms for examining patients with rash and fever

Now - special emphasis on response.

Critical Benchmarks for Bioterrorism Preparedness Program

- Timeline for developing communications system for 24/7 flow of critical health information among hospital E.D., state/local health officials, and law enforcement
- Interim plan for risk communication and information dissemination to educate the public regarding exposure risks and effective public response
- Timeline to assess training needs (e.g. emergency department personnel, I.D. specialists, public health staff, other health care providers)



Priority Benchmarks

- Plans for receipt of material from the National Pharmaceutical Stockpile and delivery of vaccines and antibiotics to entire population within 3 to 5 days.
- Hospital Surge capacity to accommodate a sudden demand made by at least 500 acutely ill patients.
- Hospital plans for isolation rooms in Emergency Departments, especially for suspect smallpox cases.



Overall Goal

HHS Bioterrorism Program

- To Ensure sustained public health and medical readiness for our communities and our nation against:
 - Bioterrorism
 - Infectious disease outbreaks
 - Other public health threats and emergencies



One Integrated Program Three Watchwords

- SPEED in making funds available for use
- FLEXABILITY in how funds are used
- ACCOUNTABILITY for results obtained



The Consequences of a Biological Weapon Attack Would be an Epidemic

Response required is fundamentally different from that demanded by natural disasters, conventional explosives, chemical terrorism or nuclear weapons



Public Health Preparedness

Why are we Concerned?

- 9/11 Aum Shinrikyo
 - Sophisticated dissident groups
- Russia, Iraq
 - Known large supplies of biological weapons
- More countries developing offensive programs
- Increasing numbers of laboratories with competence to produce agents – difficult to track
- Internet
 - Agents available from many sources
 - Manufacturing methods



"Criterion Rating" of Bioagents

Anatoliy Voroboyov - April 1994

A rating system for grouping bioagents by probability of use as biological weapons – based on an analysis of 22 agents according to different criteria.

The ideal agent would score **32 points**.

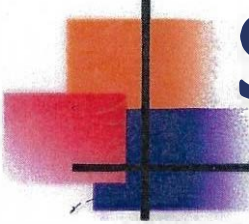
Smallpox	26	Botulism	21	Marburg	18
Plague	23	VEE	20	Influenza	17
Anthrax	21	Tularemia	20	Melioidosis	17
		Q fever	20	Typhus	15



FOR OFFICIAL USE ONLY

Populations of Groups at Increased Risk for Adverse Vaccination Events

• Cancer / Chemotherapy	9 million
• Organ Transplant	185 thousand
• HIV Infected	850 thousand
• Pregnant	6 million



MAJOR FOCUS ON STATE AND LOCAL ASSETS

(continued)

Timeliness and Quality of Initial
Engagement Determine

Course and Duration of Crisis

Character and Magnitude of
Consequences

Vaccination of High-Risk Individuals (estimates only)

- Military and some foreign-based U.S. staff
 - 2 Million people
- Emergency room staff and families
 - 1 Million + 3.5 Million = 4.5 Million
- First responders and families
 - 10 Million + 35 Million = 45 Million
- Transport workers and families_____?
- Key government officials_____?
- Workers in essential industries_____?

Attitudes Toward Bioterrorism

- Biological weapons have played no role in conflict or terrorism in this century and thus there is no reason to fear them now
- Use of such weapons is so repugnant that no one would deign to use them
- Production of organisms in sufficient quantity and in a dispersable form is not possible except in the most sophisticated laboratories
- The potential destructiveness of the major bioweapons is so great as to be unthinkable



Recent Events Which Have Changed Perceptions of the Threat (cont.)

- 1995 - Aum Shinrikyo launches sarin attack in subway which kills 12 and injures 5500. (Plans originally called for 70 tons to be used). Cult was found to be working with anthrax and botulinum organisms; had sent a team to Zaire to obtain Ebola virus. Later, it was discovered that they had made 8 attempts to aerosolize anthrax and botulinum throughout Tokyo.
 - Sect is still intact and legal
 - Net cash flow of >\$20 million per year
 - Fumihiko Joyu released from jail on Dec 29
 - Japan reports having 220,000 cults



Recent Events Which Have Changed Perceptions of the Threat

- 1995 - Iraq confirms the existence of a larger and more sophisticated bioweapons program than had hitherto been suspected despite heightened intelligence and UNSCOM teams
 - The infrastructure and expertise are still in place



Biological Weapons Programs in Year 2000

- Estimated that dozen states possess or are actively seeking offensive BW capacity - including all states named by State Department as sponsors of terrorism
- Appeal of inexpensive, asymmetric class of weapons
- Efforts by non-state actors (e.g., Aum Shinrikyo) to develop mass casualty anthrax, botulinum toxin, and Ebola bioweapons



Anthrax Available

Here are locations of 46 germ banks known to stock anthrax cultures for purchase, exchange or giveaway. Hospitals and researchers use the cultures.



Contact Vaccinia Infection

Source of Vaccinia

Age of infected patients	Siblings/ playmates	Parents/ close relatives	Son/ daughter/ grandchild	Other
0-4	75	11	0	5
5-19	21	2	0	1
20+	1	0	24*	3
Total	97**	13	24	9

*Primarily parents and grandparents

**81 siblings; 16 playmates



DHHS Office of the Secretary

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Hospitals: Central, Fragile, Inelastic

Substantive and symbolic lynchpin of U.S. health care

Financially pressured

- 1998: 1/3 in red; '99: revenue falling
- Lost 1,000 hospitals in the past decade
- Face competing demands

No surge capacity

- Just-in-time staffing and supplies
- 100-1,000 casualties would overwhelm even large centers
- Prospect of escalating, sustained burden



Smallpox Vaccine Policy

Logistical and Administrative Issues

- Practicality of identifying “smallpox hospitals”
- Logistics of administering vaccine to health care workers
- Administrative requirements to meet IND provisions
- Multi-dose vaccine vials

