Science and politics of smallpox eradication

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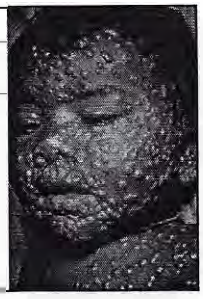
Seminar Preview

- Why the concern about smallpox?
- A brief history of the eradication program
- The threat of biological weapons
- September 16 – decision making in a crisis
- A new vaccine – what to do with it

Smallpox – Clinical Features

- Virus disease; man is the only host
- Incubation period – 10 to 17 days
- Fever, severe flu-like symptoms then rash
- Face-to-face spread only during rash
- No sub-clinical infections
- Case-fatality rate – 25 to 30%

Day 9



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 previous 3 years

Global eradication programs

Hookworm	1909-23	14 years
Yellow fever	1915-32	17 years
Yaws	1948-66	18 years
Malaria	1955-73	18 years
Smallpox	1967-80	14 years
G. worm infection	1986- ?	29 years +
Poliomyelitis	1988- ?	27 years +

Prelude to a committed effort

- 1950 PAHO Regional Director Fred Soper
  Proposes regional eradication of malaria, yaws, and smallpox
- 1953 WHO Director General Brock Chisholm
  Proposal for a program in which all countries would have a major concern
- 1958 USSR proposes global eradication
  Viktor Zhdanov
- 1958-66 Limited resources

The first serious effort

Assembly requires DG to submit a plan –1966

- Strategy
  Vaccination of 80% of population
  Surveillance and containment program
- 10 year program WHO budget =$ 2.4 million/year
- Objections by delegates
  - Not feasible; malaria eradication is failing
  - Demand for no further increases in WHO budget
- 58 votes needed; 60 voted for approval

Program leadership

- Director General believes program will fail
  (malaria eradication program collapsing)
- Demands an American serve as Director
  The candidate declines:
  CDC West Africa smallpox-measles program
  Limited resources – <$50,000 each for 50 countries
  Not enough to buy the vaccine required
  The U.S. Surgeon-General decides
- Relationships: WHO/USSR/USA

The Challenge

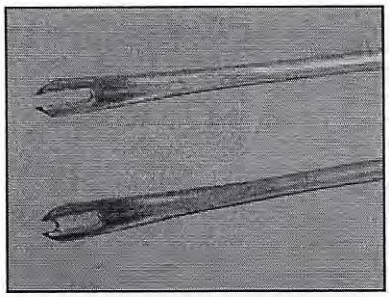
- Status of smallpox – 1967
  >10,000,000 cases
  2,000,000 deaths
  43 countries reported cases
- Program staff
  Headquarters – 8 professional and 3 secretaries
  International staff – never more than 150
  (WHO, CDC, Peace Corps)
  National staff – variable up to 150,000

Key elements in smallpox eradication
a better vaccine and vaccination method

Critical need – a heat stable vaccine
- Process for commercial freeze drying – 1953

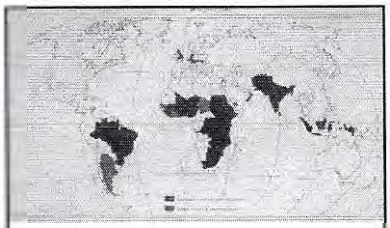
Potency and purity standards for vaccine
- WHO Committees – 1958
- Standard production manual -- 1968
- Testing laboratories – Netherlands, Canada – 1969
- Vaccine needed – 250 million doses/year

The bifurcated needle
- Invented by Ben Rubin – 1964



The strategy

- Vaccination of 80% -- quality control teams
- Surveillance
  To obtain a weekly report from every health center and hospital
- Containment
  "Fire-fighting teams"
  Investigate every case
  Cut chains of transmission with ring-vaccination



■ = Endemic countries
▩ = Others with cases

Smallpox 1967

Ali Maalin - 26 October 1977

After eradication is certified - May 1980

- Vaccination ceased in all countries--1980
  - U.S. stopped routine vaccination – 1972
- Manufacturers dismantled facilities
- Research programs sharply reduced
  Perhaps 4 to 6 staff in each of two labs
- Vaccine availability (as of 1998)
  - Total for all countries-- ? 90 million doses

Variola virus destruction proposed by WHO Expert Committee

- Committee deliberations -- 1985 to 1994
  Representative strains sequenced and archived
  Destruction of smallpox strains recommended
- Endorsed by 5 international microbiol. orgs.
  Strong support by developing countries
- Proposed Assembly resolution – 1995
  Strong objections by one department of U.S.A.
  Deferred 5 times at WHAs "in order to permit additional vaccine and antiviral research"
- "Final" vote to be taken ? 2018

Biological weapons threat – 1990s

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

New realities -- Sept. 11, 2001

Meeting with Secretary Thompson– Sept. 16

- Possible second attack--smallpox
- U.S. susceptibility to smallpox-- ~ 75%
  - No routine vaccination for 30+ years
  - Protection waning among prior vaccinees

Suppose that the shoe drops tomorrow

Vaccine supply--a high priority

September 17, 2001

Epidemic smallpox cannot be stopped without vaccine

- Vaccine manufacturers
  - U.S. and world -- None
- Vaccine in U.S. storage – 15 million doses
  - Available for shipment 90,000 doses
    - diluent had gone bad

Emergency task force to resolve issues

- Informal policy group of ~ 10
  - Secretary and a senior advisor
  - Experts in vaccine development and delivery
  - Knowledgeable veterans of government bureaucracy
- Regular briefings - CDC, FDA, NIH, DoD, Industry

(Note: *not a formal inter-agency working group*)

Short term options and problems

- Can we dilute the vaccine -- if so, how much?
  - Special studies would be needed – and time
- How do we obtain vaccine more rapidly than industry's estimate of 6 years?
- What about tissue culture rather than calves?
  - Could research laboratories produce vaccine?
- If we have an attack in the interim, what do we do?

Vaccine emergency resolution

- Vaccine produced in tissue culture - ACAM2000
  - 250 million doses in 18 months.
  - Grown by Baxter in Austria; packaged in U.S.
  - Human subjects trials satisfactory but another 3 years of studies necessary before licensure
- Emergency use authorized by new legislation

Frequency of Adverse Reactions

ACAM2000

Life-threatening complications (per million)

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

Less serious

- Accidental inoculation, rash, fever

Myopericarditis

- 1.3 cases per 1000, mild, few sequelae

A second vaccine-- Lc16m8

produced by Kaketsuken, Japan

- Derived from Lister vaccine strain
  - Attenuated virus grown in tissue cell culture (termed a third generation vaccine)
  - Heat stable, administered by bifurcated needle
  - Virus replicates postvaccination, like ACAM2000
  - Safety tested in more than 70,000 children
  - Licensed in Japan

U.S. insists on new vaccine, anti-virals before smallpox virus is destroyed

Goals proposed by U.S. delegation-- 2002

- A vaccine equivalent to ACAM 2000 in efficacy and heat stability but has no adverse effects

Eventual product: Imvamune (Modified Vaccinia Ankara, MVA)

- Two anti-viral products which have different modes of action, for use in treatment of cases

New products: Tecovirimat, brincidofovir

Imvamune – the new product

- R&D costs – primarily provided by U.S. govt.
- Vaccine purchased from Bavarian-Nordic
  - Cost to produce and maintain a 20 million dose stockpile -- $777 million
  - Stated cost of 2 vaccine doses required per vaccinee -- $52
- Technical challenges
  - Shelf-life -- 2 years at -20° C.
  - In-use shelf-life – 12 hrs. @ 2° to 8° C. in the dark

Imvamune – fatal problems

- Administrative use issues
  - Rapid smallpox outbreak containment is critical
    Imvamune requires 2 doses 28 days apart (full protection achieved 42 days after first dose)
  - Safety uncertain -- only 7400 subjects tested
  - Monkey study findings after virus challenge transmission after one dose—implies possibility of spread of smallpox from persons with no outward sign of infection

Anti-virals: Tecovirimat, brincidovir

- At this time, no practical prospective use of these antivirals is foreseen
- Lack of animal pox virus models makes treatment studies uninterpretable.
- Cost and management issues limit the potential use of anti-virals to patients with rash – 3+ days after fever

WHO meeting on vaccine and use

SAGE Committee on Immunization–Nov 2013

- Vaccines recommended for stockpile use
  - Meet WHO standards for potency, purity, stability
  - Lyophilized
  - Can be administered by bifurcated needle
  - Produce a visible major cutaneous reaction as a correlate of protection
  - ACAM2000 and IC16m8 for WHO stockpile

Note: MVA-Imvamune not recommended pending more data on safety and efficacy

Vaccine availability

- Status of stockpiles—number of doses
  - WHO emergency stockpile 31 million
  - U.S. <220
  - Russia, China ??
  - Other countries 350-400
    Total 600-650 million
- Vaccine production capacity
  Kaketsukan (Japan) 80 million/year
  SanofiPasteur contracted facility – Still trying
  Decision for CDC to contract for U.S. producer --2008

Reflections on progress

- 20 years have elapsed since a WHO Expert Committee recommended to the Assembly that the remaining stocks of variola virus be destroyed
- 14 years have elapsed since the 9/11 attack and response plans began to be formulated
- 12 years since a WHO Committee recommended that there be a 200 million dose WHO emergency stockpile and at least 2 large-scale manufacturers

What to do if there is an outbreak reported in Spain---and 3 U.S. returned visitors with rash?