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ANTHRAX AND OTHER VACCINES: USE IN THE U.S. MILITARY

Anna Johnson-Winegar, Ph.D.

Deputy Assistant to the Secretary of Defense for Chemical and Biological Defense

Joint Statistical Meeting 2001:
Anthrax and Other Vaccines: Just the Stats

Sponsored by the Committee on Statisticians in Defense and National Security

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Outline

- **DoD BD Vaccine Program**
  - Research
  - Development
  - Production
- **FDA Licensure**
  - IND, Efficacy, Animal Models, Surrogate markers
- **Anthrax Vaccine**
  - Safety
  - Potency (Testing, Immunogenicity)
- **Developmental Vaccines**
  - rPA, Smallpox, Plague, etc.
  - Multivalent & Multiagent Vaccines
- **Vaccination decisions**
  - Risks: Vaccination effects *vs.* disease effects
  - Multiple vaccinations and interactions
- **Alternatives to Vaccination**
  - Protection
  - Post-exposure therapy

Some Statistics about Anthrax…

- Approximate inhaled dose to cause infection: **8,000 – 20,000 spores**
- Typical incubation period: **1-7 days**
- Typical duration of illness: **3-5 days**
- Population likely to die once symptoms have appeared following exposure to inhalational anthrax: **>95%**
- Approximate quantity of anthrax spores accidentally released in Sverdlovsk, Russia in 1979: **4 mg**
- Number of fatalities following the accidental release: **68**
- Naturally occurring cases of inhalation anthrax in the United States: **0**
  - 18 cases of inhalation anthrax in the U.S. since 1900, last in 1976.
  - 2 cases of gastro-intestinal anthrax in 2000 (recovered without treatment).

…and the Anthrax Vaccine

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- Number of licensed biodefense vaccines in production: **1**
- Date of FDA licensure of AVA: **1970**
- Number of doses required for full immunity: **6**
- Number of studies (involving 366,000 recipients) validating the safety of the current vaccine: **13**
- Reported vaccine adverse events:
  (VAERS data for those probably or certainly linked to the vaccine as of 25 April 2001)
  - Other than serious: 0.14% (709 of 508,709)
  - Serious: 0.017% (86 of 508,709)
    (Serious = loss of duty >= 24 hours, not hospitalized)
  - Hospitalization: 0.0022% (11 of 508,709)
  - **Total Adverse Events: 0.16%** (806 of 508,709)

Anthrax Vaccine Efficacy against Inhalation Challenge

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- Efficacy of current vaccine based on bacterial construct (that is, Protective Antigen binding to Lethal Factor and Edema Factor) not on route of exposure.
- Brachman study suggests efficacy in humans against inhalational anthrax
  - 5 cases of inhalational anthrax (4 fatal) among non-vaccinated individuals (n =754)
  - Zero cases of inhalation anthrax among vaccinated individuals (n = 379)

Vaccine Efficacy Against Aerosol Challenge

	Vaccinated		Control	
	Number	Percentage	Number	Percentage
Rabbits	62 of 65	**95**	0 of 18	**0**
Rhesus Macaques	114 of 117	**97**	0 of 28	**0**

Potency Testing

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- **Potency is assessed by survival of vaccinated laboratory animals after lethal challenge.**
- **Each lot must meet the following potency criteria:**
  - Follows 21 CFR 610.10 guidelines.
  - Potency is determined in the following manner:
    - Three serial dilutions of vaccine are used plus one control group (no vaccine) to vaccinate guinea pigs;
    - 14 days after vaccination, all guinea pigs are injected with known amounts of virulent anthrax;
    - Average time to death is calculated for each group; and the passing result is that the test vaccine is no less potent than the reference vaccine.
    - Two vials per lot are tested for potency.

Assessing Risk

- Number of attacks against the U.S. military personnel with anthrax (or any biological weapon): **0**

- Probability (P) of attacks in the future against the U.S. military personnel with anthrax (or any biological weapon): **$0 \leq P \leq 1$**

Why Vaccinate?

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- **Biological warfare (BW) agents pose high risk to military forces and operations**
  - At least 10 countries pursuing BW programs
- **Vaccines are lowest risk, most effective protection**
  - More effective with fewer adverse effects than antibiotics or other treatments
  - Enable force projection by providing continuous, long-lasting protection
- **No real-time detection systems currently available**
  - Identification delayed 15-45 minutes after exposure
- **Masks must be worn to be effective**

Vaccine Use Risk Management Decisions

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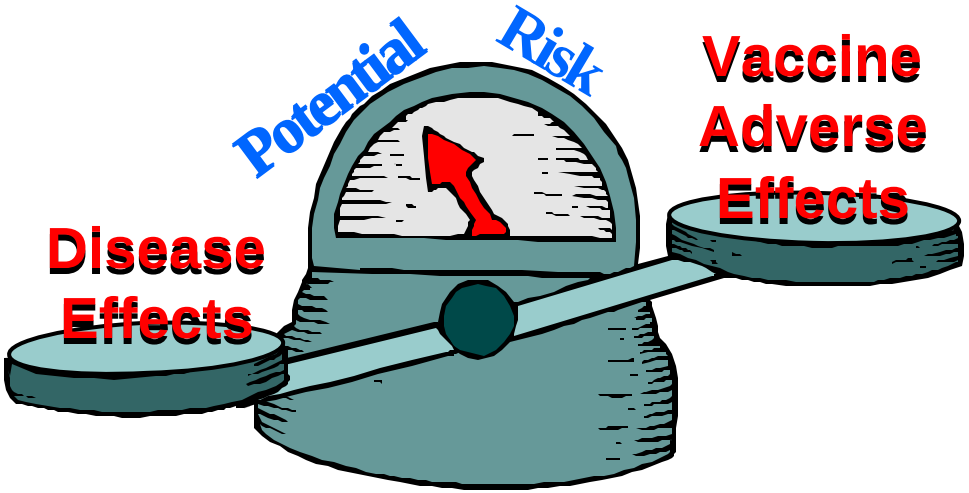
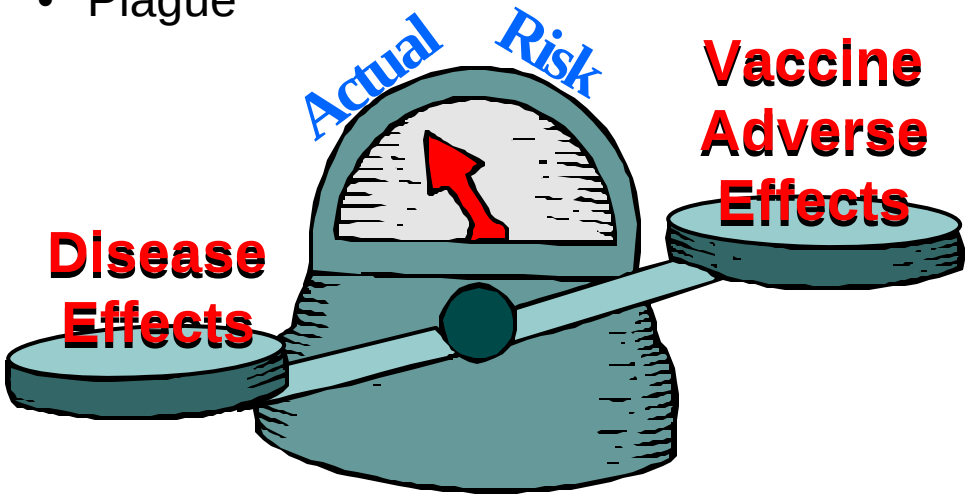
Naturally-Occurring Infectious Diseases

(Selected Prophylaxes)

- Typhoid
- Yellow fever
- Malaria
- Diphtheria
- Tetanus
- Poliovirus
- Plague
- Hepatitis A virus
- Meningococcal disease
- Influenza vaccine
- Measles
- Mumps
- Rubella





Biological Defense Vaccines

- Anthrax Vaccine Adsorbed
- Botulinum Toxoids*
- Tularemia Vaccine*
- Smallpox vaccine (Vaccinia Virus, Cell Culture-derived)*
- Equine Encephalitis Virus Vaccines*

**Investigational New Drug (IND) status*

A Complete and Comprehensive List of Risk-Free Military Operations and Activities

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Concerns for Developing & Producing Biological Defense Vaccines

- **Limited interest from industry**
  - Most Public Health needs are fulfilled by the private sector
  - BD Vaccines similar to orphan drugs (interest from a few small to mid-size companies)
- **Identifying surrogate markers of efficacy**
  - Animal models used to validate efficacy of vaccines
  - Limited human efficacy data available
    - FDA review of 21 CFR requirement for Phase 3 efficacy testing in humans
    - May allow efficacy based on animal data (at least two species)
- **Large/complicated clinical studies to demonstrate safety, immunogenicity, and efficacy**

Concerns for Using Biological Defense Vaccines

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- **Vaccine use: Routine use *vs.* stockpile**
  - Limited shelf life for stockpile
  - FDA issues for maintaining license if site not involved in ongoing production
- **Undetermined health effects of administering multiple vaccines**
  - No adequate basis to assess safety, yet no basis for extraordinary concern
    - *Interactions of Drugs, Biologics, and Chemicals in U.S. Military Forces* (1996) Institute of Medicine
- **Undetermined long-term health & safety effects**
- **Policy/Risk decision on vaccine types**
  - Live vaccines may be more effective, yet may have greater adverse effects (*e.g.*, Oral *vs.* injectable polio vaccines)
- **No policy for immunizing civilian population**
  - Considerations include larger populations, pediatrics, geriatrics, immune-suppressed individuals

Medical Countermeasures against Biological Warfare Agents

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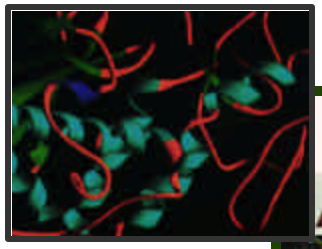
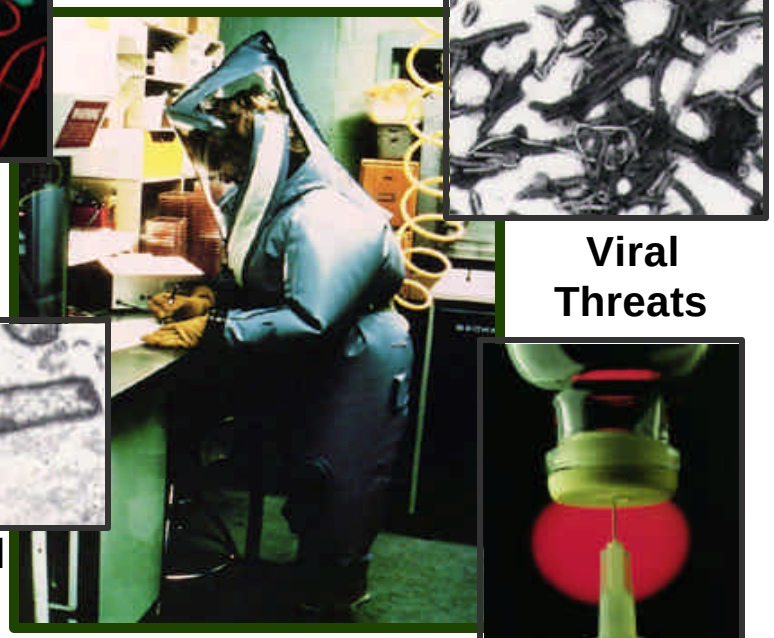
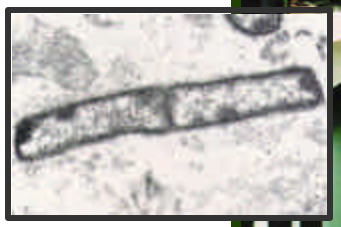


Toxin Threats



Viral Threats



Bacterial Threats

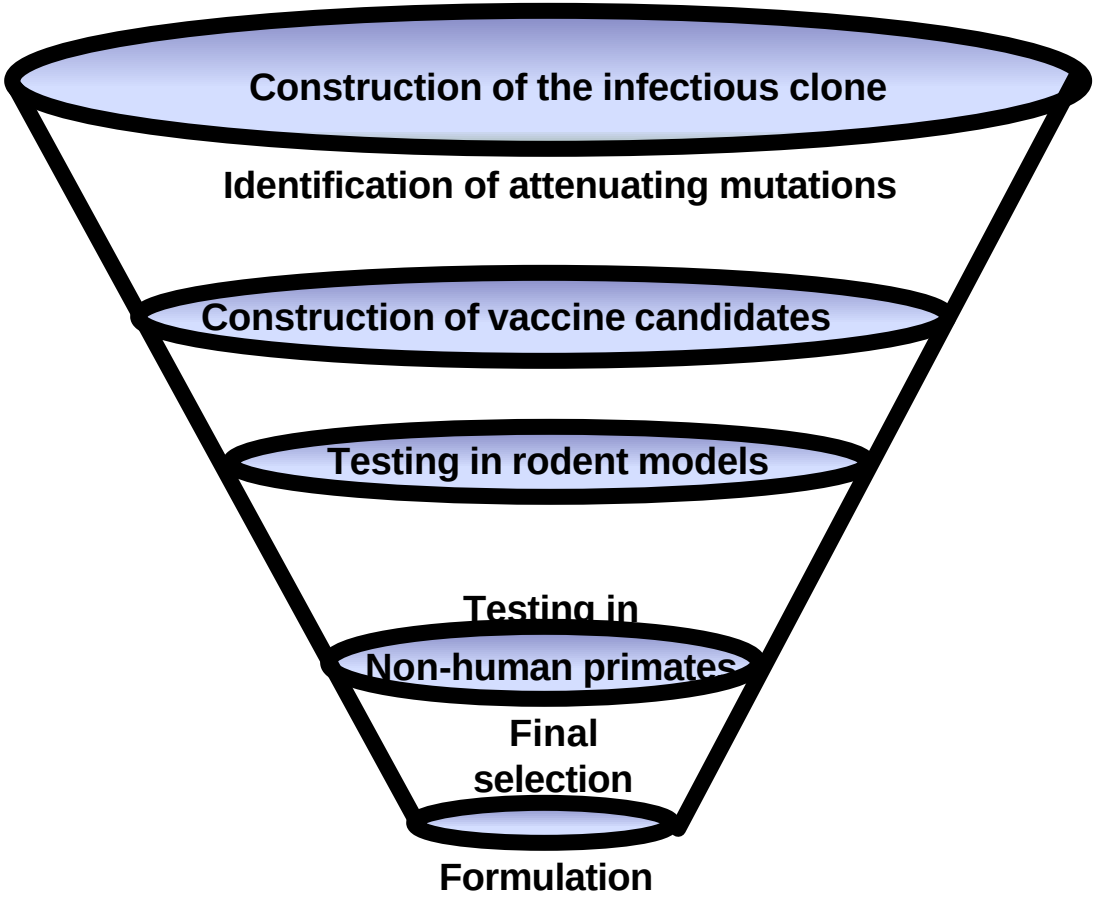
Medical BioDefense Research Program (MBDRP) Efforts → MBDRP Products

Technical Approach:

- Identify mechanisms involved in disease process.
- Develop and evaluate products (vaccines or drugs) to prevent or counter effects of toxins, bacteria, and viruses.
- Develop methods to measure effectiveness of countermeasures in animal models that predict human response.
- Develop diagnostic systems and reagents.

MBDRP Research Areas

- Virology
- Bacteriology
- Toxinology
- Genetically Engineered Threats



Next Generation Anthrax Vaccine

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- **Vaccine based on recombinant protective antigen (rPA), which binds to the Lethal Factor (LF) and Edema Factor (EF) of *B. anthracis***
- **rPA would provide ^{3} protection, would require fewer doses to produce immunity, and have fewer adverse effects than current vaccine**
- **Recombinant production technology would eliminate need for spore-forming anthrax**
- **Reduced requirement for number of vaccines or immunization schedules = greater flexibility and fewer time constraints in fielding a protected force.**
- **Decreased production cost, greater range of potential vaccine production facilities, and potential for regulatory streamlining of the vaccine carrier.**

Joint Vaccine Acquisition Program

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- **Mission:**
  - Transition candidate biological defense vaccines from research laboratories to a Prime Systems Contractor:
    - Development
    - Testing
    - FDA licensure
    - Production and storage of vaccine stockpiles for use by all services.
  - A major objective of the program is to establish a viable industrial base for vaccine production.
- **Prime Systems Contract awarded in November 1997 (DynPort Vaccine Production Corporation, LLC)**

Joint Vaccine Acquisition Program
Vaccines

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- Smallpox
- Plague
- Pentavalent Botulinum Toxoid
- Tularemia
- Next Generation Anthrax
- Ricin toxoid
- Options for 11 additional vaccines

Parting Thoughts

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- **Availability of vaccine based on several factors:**
  - Sustained resources to transition products from tech base and advanced development
  - FDA licensure of vaccine and production facility
  - Commercial interest likely to be limited – Biological Defense (BD) vaccines similar to orphan drugs
- **Implementation of vaccination**
  - Vaccination decisions will continue to have greater physiological consequences than non-medical (*e.g.*, mask on) decisions
  - Risk communication as important (if not more) than risk assessment

Backup Slides

What Does Producing a Vaccine Mean?

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	SCIENCE & TECHNOLOGY	DEVELOPMENT & LICENSURE	LICENSED PRODUCTION
Production Approach	Bench top – many approaches	Scale up – best approach	Full Scale – fixed method
Vaccine Recipients	Lab animals (10^2-10^3)	Volunteers (10^3)	Population (10^6)
Data Management	Lab notebook	Master File: mfrng and release data, clinical trials, validation studies	Mfrng and release data, post market surveillance, adverse reactions
Stakeholders	Scientist, science manager, User	Scientist, product mgr., FDA, manufacturer, User	Warfighter, medic, logistician, FDA, mfr., product mgr.
Production Risk	Moderate	High	Low
Overall Risk	Low	High	Low–High

Anthrax Vaccine Adsorbed (AVA)

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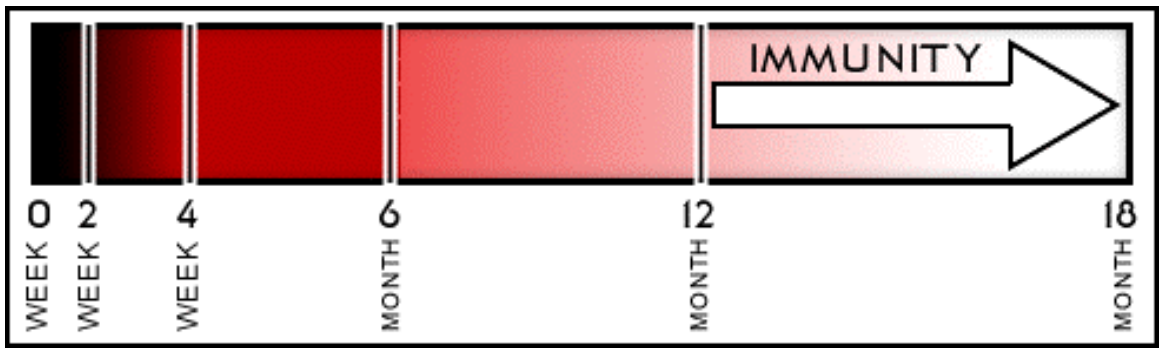
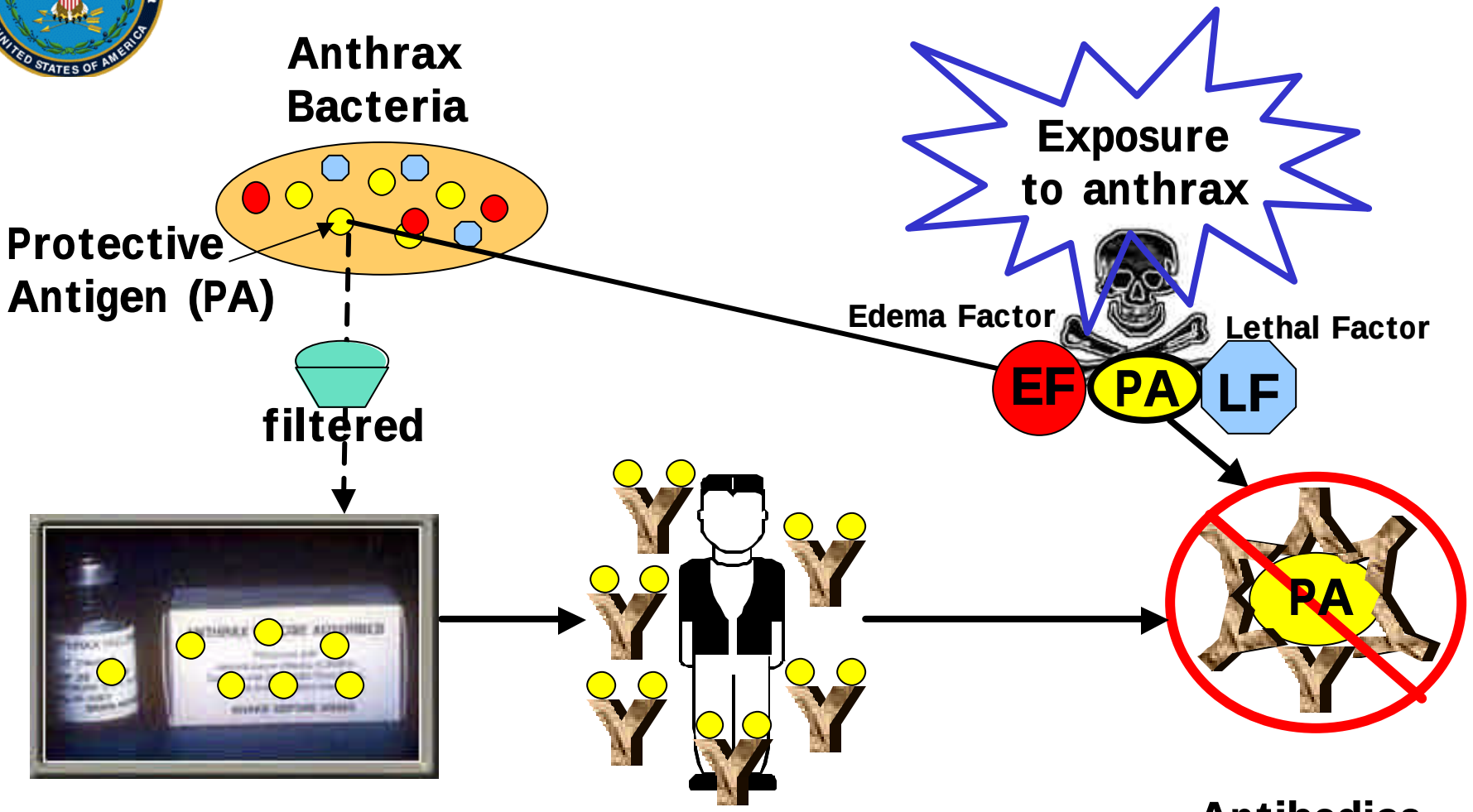
- Approved by the FDA in 1970 (Only licensed BD vaccine)
- Cell-free filtrate, produced by a strain of anthrax that does not cause disease.
- Safely and routinely administered to at-risk wool mill workers, veterinarians, laboratory workers, and livestock handlers in the United States
- Manufactured by BioPort Corporation
- Currently requires 6 shots & annual booster to maintain full immunity



How Anthrax Vaccine Prevents Disease



Vaccine contains PA, extracted from anthrax bacteria.

Immune system develops antibodies (Y) to PA, protection from disease.

Antibodies "neutralize" PA, common part of anthrax toxins.

Implementation of the Anthrax Vaccination Program for the Total Force

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- **December 15, 1997: SECDEF approves decision contingent on the successful completion of four conditions:**
  - Supplemental testing of the vaccine;
  - Assured tracking of immunizations;
  - Approved operational and communications plans; and
  - Review of health and medical aspects of the program by an independent expert

- **May 18, 1998: SECDEF directs vaccination of total force**

- **Implementation consistent with DoD Directive 6205.3, "DoD Immunization Program for Biological Warfare Defense" (November 26, 1993)**

Anthrax Vaccination Status
(as of 29 May 2001)

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>2,000,000 doses administered.
>500,000 have received initial shots.
>70,000 personnel have received entire shot series.

	Army	Air Force	Navy	Marines	Coast Guard	Archived	Total
Shot #1	152,000	143,484	99,539	74,847	576	40,606	511,052
Shot #2	144,074	138,228	91,411	71,915	547	36,997	483,172
Shot #3	135,302	132,868	84,811	68,284	517	36,865	458,647
Shot #4	108,827	98,189	49,953	49,431	349	23,139	329,888
Shot #5	71,133	62,676	22,307	28,029	139	11,658	195,942
Shot #6	30,122	28,166	5,219	4,665	20	3,652	71,844
Annual Booster	1,631	697	1	0	0	54	2,383
Total	**643,089**	**604,308**	**353,241**	**297,171**	**2,148**	**152,971**	**2,052,928**

* NOTE: "Archived Immunizations" includes all immunizations administered to individuals who have left active service.

The "TOTAL" column now reflects running totals of all immunizations administered since the beginning of the AVIP in March 1998.

Form VAERS-1 Reports

(as of 25 April 2001)

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***508,709** people had been vaccinated with **2,043,009** doses of anthrax vaccine.*

Reports Reviewed by the Anthrax Vaccine Expert Committee (AVEC) [a]				
Total Unique Form VAERS-1 Reviewed Through 03 Apr 01[b]	Reports Other Than Serious (no loss of duty =/>24 hrs nor hospitalized)	Loss of Duty =/>24 hours (not hospitalized)	Hospitalized	
1530 [c]	1329	146	55	Total Reports
806	709	86 [d]	11 [e]	Certainly or probably caused by anthrax vaccine

[a] AVEC, a panel of civilian academic medical experts sponsored by the Health Resources & Services Administration of the U.S. Department of Health & Human Services, meets every 4 to 6 weeks.

[b] VAERS-1 forms record events that happen after vaccination. Some events are caused by the vaccine, some are not.

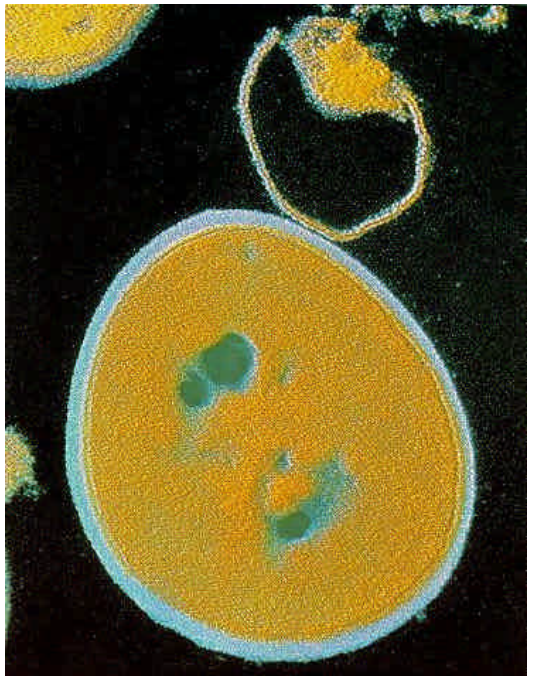
[c] Excludes 20 duplicate reports for a total of 1550 VAERS-1 forms reviewed; represents VAERS-1 forms for 1472 individuals.

[d] Includes injection-site reactions (50), acute allergic reaction (9), rash (9), "flu" like symptoms (8), gastroenteritis (2), myalgia (2), pruritus (2), bronchiolitis obliterans (1), paresthesia (1), photophobia (1), swollen lymph node (1)

[e] All eleven were allergic, inflammation reactions at injection site.

Medical Biological Defense:
Current Capabilities – Therapeutics

- **Therapeutics**
  - Various antibiotics for treatment of exposure to bacterial agents
    - Ciprofloxacin
    - Doxycycline
    - Tetracycline



Cell wall destroyed by antibiotic