Biological Weapons and Bioterrorism Threats: The role of vaccines in protecting the military and civilian sectors

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Biological Weapons and Bioterrorism Threats: The Role of Vaccines in Protecting the Military and Civilian Sectors

The original document contains color images.
Outline

- Threats
- DoD Medical Biological Defense Capabilities
- Responses
  - Military
  - Civilian
# Potential BW Threats

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Virus</th>
<th>Toxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthrax</td>
<td>Smallpox</td>
<td>Botulinum (Types A-F)</td>
</tr>
<tr>
<td>Plague</td>
<td>Encephalomyelitis</td>
<td>Staphylococcal Entertoxins (SEB)</td>
</tr>
<tr>
<td>Tularemia</td>
<td>Ebola</td>
<td>Ricin</td>
</tr>
<tr>
<td>Brucellosis</td>
<td>Marburg</td>
<td>Marine Neurotoxins</td>
</tr>
<tr>
<td>Q-Fever</td>
<td></td>
<td>Mycotoxins</td>
</tr>
<tr>
<td>Glanders</td>
<td></td>
<td>Clostridium Perfringens</td>
</tr>
<tr>
<td>Cholera</td>
<td></td>
<td></td>
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<tr>
<td>Typhus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shigellosis</td>
<td></td>
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</tr>
</tbody>
</table>
Bioterrorism Threats

…to reality.
Why Vaccinate?

- **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**
Requirement

- DoD policy stated in DoD Directive 6205.3 to “...develop a capability to acquire and stockpile adequate quantities of vaccines to protect the programmed force against all validated biological warfare threats.”
Chronology of Considerations for BD Vaccine Production

**1991/92**

**GOCO**
- *Why Started?* Lessons From ODSS
  - No Surge Capacity for BD Vaccines
  - Limited Industry Interest
- *Why Stopped?* DOD and Congressional Directives
  - Need for Dedicated DOD Facility?
  - Most Economical Approach?

**June 93**

**COCO**
- *Why Modified?* Affordability
  - ADM Directed Cost/Benefit Analysis
  - $450M Unfunded Requirement FY96-01
  - Industry Survey

**Aug 94**

**Prime Systems Contract Approach**
- *Why Started?* Optimum Resource Utilization
  - Reduces Requirement for New Facilitization
  - Enhances Competition
- Directed Prime Systems Contract Approach
- Prime System Contract Awarded (Nov-1997)

**Jan 95**

**1996**

(Joint Program Office for Biological Defense Established)
What Does Producing a Vaccine Mean?

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

- 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
  - Study underway by CDC to investigate fewer doses in series (reduce to 3-4 shots)
**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.
### Anthrax Vaccine Efficacy against Inhalation Challenge

- 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

<table>
<thead>
<tr>
<th></th>
<th>Vaccinated</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percentage</td>
</tr>
<tr>
<td>Rabbits</td>
<td>62 of 65</td>
<td>95</td>
</tr>
<tr>
<td>Rhesus Macaques</td>
<td>114 of 117</td>
<td>97</td>
</tr>
</tbody>
</table>
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**
Commercial Sector Concerns

- Unusually hazardous risks, liability and indemnification issues
- Small volume of business and low annual production requirements
- Limited commercial opportunities for BD vaccines
- Stringent Bio-containment requirements
- Biological Warfare Convention inspection requirements
- Government contracting and regulatory oversight requirements
Key Features of a National Vaccine Production Facility

- Government control of production, availability, and distribution
- Meets high national security priority for additional BD vaccine production
- Establishes a second source for anthrax vaccine adsorbed (AVA) production
- Overcomes limited industry interest in BD vaccine production
- Gov’t biosafety containment facilities provide supporting R&D
- Flexibility for emerging production technologies
- Operating contractor provides specialized expertise in vaccine production and regulatory requirements
Challenges

- Defining production capacity requirements
- Defining battlefield exposure levels for Biological Warfare (BW) agents
- Addressing emerging/changing requirements
  - FDA regulations
  - DoD policy
- Cooperative development with potential international and domestic partners
  - Aligning requirements
  - Negotiating agreements
  - Avoiding schedule impacts
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): $0 \leq P \leq 1$
Vaccine Use Risk Management Decisions

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
Limitations on Military Material Support for Civilians

- Material designed to meet warfighter requirements may not be suitable for civilian use.
  - Medical products must be fully licensed by the Food and Drug Administration and/or used with individual informed consent.
  - Military medical CB defense products assume a healthy adult population.
  - Some CB defense vaccines, pretreatments, and treatments may confound other medical treatments.
  - Classic “benefit-to-risk” decisions are not likely to support pre-exposure immunization of large populations against biological agents.
  - Voluntary compliance cannot be guaranteed for a large population.
Concerns for Using Biological Defense Vaccines

• **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
Parting Thoughts

- **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