Draft Recommendations for the Use of Anthrax Vaccine Adsorbed

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On behalf of the
ACIP Anthrax Vaccine Work Group

October 23, 2008

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Outline of Session

- I. Statement Outline
- 2. Use of AVA
- 3. Pre-event recommendations
- 4. Vote
- 5. Delayed Dosing
- 6. Vote
- 7. Post-exposure prophylaxis (PEP)
- 8. Vote
- 9. PEP for repeated occupational exposures
- 10. Vote
- 11. Pregnancy Data
- 12. Vote - pregnancy/breast-feeding recommendations

Outline of Draft Statement

- Summary
- I. Introduction
- II. Methods
- III. Epidemiology of Anthrax
  - Naturally Occurring
  - Bioterrorism Related
- IV. Pathogenesis
- V. Disease
- VI. Persons at Risk
- VII. Control and Prevention
  - Immunogenicity, efficacy, safety data
  - Pregnant/breastfeeding women data

Outline of New Statement

- VIII. Post-Exposure Prophylaxis
  - Vaccine/Antimicrobial data
- IX. Recommended Uses of AVA
  - Pre-exposure
  - Post-Exposure Prophylaxis
- X. Bioterrorism Preparedness
- XI. Future Vaccines
- XII. Future Research Agenda

Anthrax Vaccine History

- 1950s: Ft. Detrick ("Merck" formulation)
  - Cell culture filtrate; precipitated with alum
  - Brachman study*
- 1960s: "Lansing" formulation
  - Manufacturing process improved
- 1970s: "Lansing" formulation licensed
  - Used data from Brachman studies
- Current: Anthrax Vaccine Adsorbed (AVA)
  - Manufactured by Emergent BioSolutions

* Brachman et al. Am J Pub Hlth 1962;52:632.

Use of AVA

- Pre-event
  - Prior to potential bioterrorism event
  - Pre-exposure
    - Prior to potential occupational exposure
    - i.e., laboratorians engaged in *B anthracis* research
- Post-exposure
  - Following a bioterrorism event (post-event)
  - For persons exposed to *B anthracis* spores, at risk for inhalation anthrax development

Pre-event Schedule

- Previous FDA licensed regimen
  - 6 dose priming series over 18 months
    - 0, 2, 4 weeks; 6, 12, 18 months
  - Subcutaneous administration
  - Annual boosters
- BLA supplement under consideration
  - Suspense date December 11, 2008

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ACIP 2000 Recommendations
Pre-Event Vaccination

- **Indicated for persons engaged in work/activities:**
  - **Involving production quantities or concentrations of *B. anthracis* cultures with a high potential for aerosol production**
- **May be indicated:**
  - **For persons in otherwise low risk occupations (i.e., persons handling animals or animal products)**
  - **For groups for whom a calculable risk can be quantified (i.e., military, other select populations)**
- **Not recommended for**
  - **First responders, federal responders, medical practitioners and private citizens**
- **Recommended PEP for personnel working in areas of a known previous release**

*CDC. Use of Anthrax Vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 2000 Dec 15;49(RR15):1-20.

ACIP 2002 Recommendations
Pre-Event Vaccination

- Amid concerns of a limited supply of vaccine "ACIP recommends that groups at risk for repeated exposures should be given priority for pre-exposure vaccination"
  - Specific laboratory personnel
  - Workers making repeated entries into known *B. anthracis*-spore-contaminated areas or where repeated exposure to aerosolized *B. anthracis* spores might occur
- "For persons not at risk for repeated exposures to aerosolized *B. anthracis* spores through their occupation, pre-exposure vaccination with anthrax vaccine is not recommended."

*CDC. Use of Anthrax Vaccine in Response to Terrorism: Supplemental Recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 2002 Nov 15;51(45):1024-6.

Issues Considered
Pre-event AVA Administration

- Burden of disease
- Risk
- Vaccine safety
- Vaccine efficacy
- Vaccine supply

Anthrax Burden of Disease

- Natural occurrence
  - Virtually no human disease in US
- Bioterrorism related
  - 1979, accidental release, Sverdlosk
  - 2001, bioterrorism event, US

Issues Considered
Pre-event Administration

	+/-
Burden of Disease	-/+
Risk of exposure	
Safety	
Efficacy	
Supply	

+ Favors pre-event vaccine
- Does not favor pre-event vaccine

Occupational Risk from Bioterrorism Exposure, Undefinable

- Varies by location in country
- Always evolving
- Time dependent
- Varies by occupation
  - ACIP draft recommendations vary by occupation

Issues Considered
Pre-event Administration

	+/-
Burden of Disease	-/+
Risk of exposure	+/-
Safety	
Efficacy	
Supply	

+ Favors pre-event vaccine
- Does not favor pre-event vaccine

Summary of AVA Safety Data

- Published reviews conclude the vaccine is safe
  - 7 independent reviews since 1985*
  - >35 published studies
- Military experience
  - >7.2 million doses to ~1.9 million people March 1998-January 2008
- Ongoing clinical trial
  - SQ administration- rates of injection site adverse events similar to other vaccines
    - Further diminished with IM administration
- Potential for rare adverse events (AEs) to occur

AVA Safety Comparisons*

	Fever(%)	Systemic(%)	Erythema or Swelling(%)	Pain, Any(%)
Acellular pertussis	0 - 7	17 – 29	12 – 15	51 – 77
Hepatitis A	0 - 3	4 - 22	4 – 40	40 – 52
Hepatitis B	0 - 4	10	1 – 99	11 - 43
Influenza	1 - 13	11 - 34	11 – 21	24 – 86
Rabies	2 - 18	3	1 – 18	4 – 52
Tetanus - diphtheria (Td)	1 - 9	17 - 26	22 – 35	43 - 85
Anthrax (SQ)	1 - 8	1 - 36	3 - 42	67 - 83

*IOM report, 2002
Slide courtesy of Col Cieslak

Issues Considered
Pre-event Administration

	+/-
Burden of Disease	-/+
Risk of exposure	+/-
Safety	+
Efficacy	
Supply	

+ Favors pre-event vaccine
- Does not favor pre-event vaccine

Brachman AVA Vaccine Efficacy Study*

- Conducted in wool mills, late 1950s
- 26 cases of anthrax
  - 0 cases among vaccinated persons
  - 5 cases (4 fatal) in unvaccinated persons
- Combined Efficacy: 92.5% (95% CI: 65-100%)

- Best evidence for efficacy of vaccine**

**Am J Public Health* 1962;52:632

***Federal Register* 1985; 50:51002
**IOM report, 2002

WG Review of Additional Efficacy Data

- CDC data collected from 1962-1974[1]
  - "These observations lend further support to the effectiveness of the product."; "…sufficient evidence to conclude that anthrax vaccine is…effective."
- IOM report[2]
  - Effective vaccine to protect against anthrax, including inhalational anthrax
  - Effective against all known strains of anthrax plus against bioengineered strains
- Ongoing AVA Clinical Trial[3]
  - Compelling immunogenicity data
  - Robust immune response

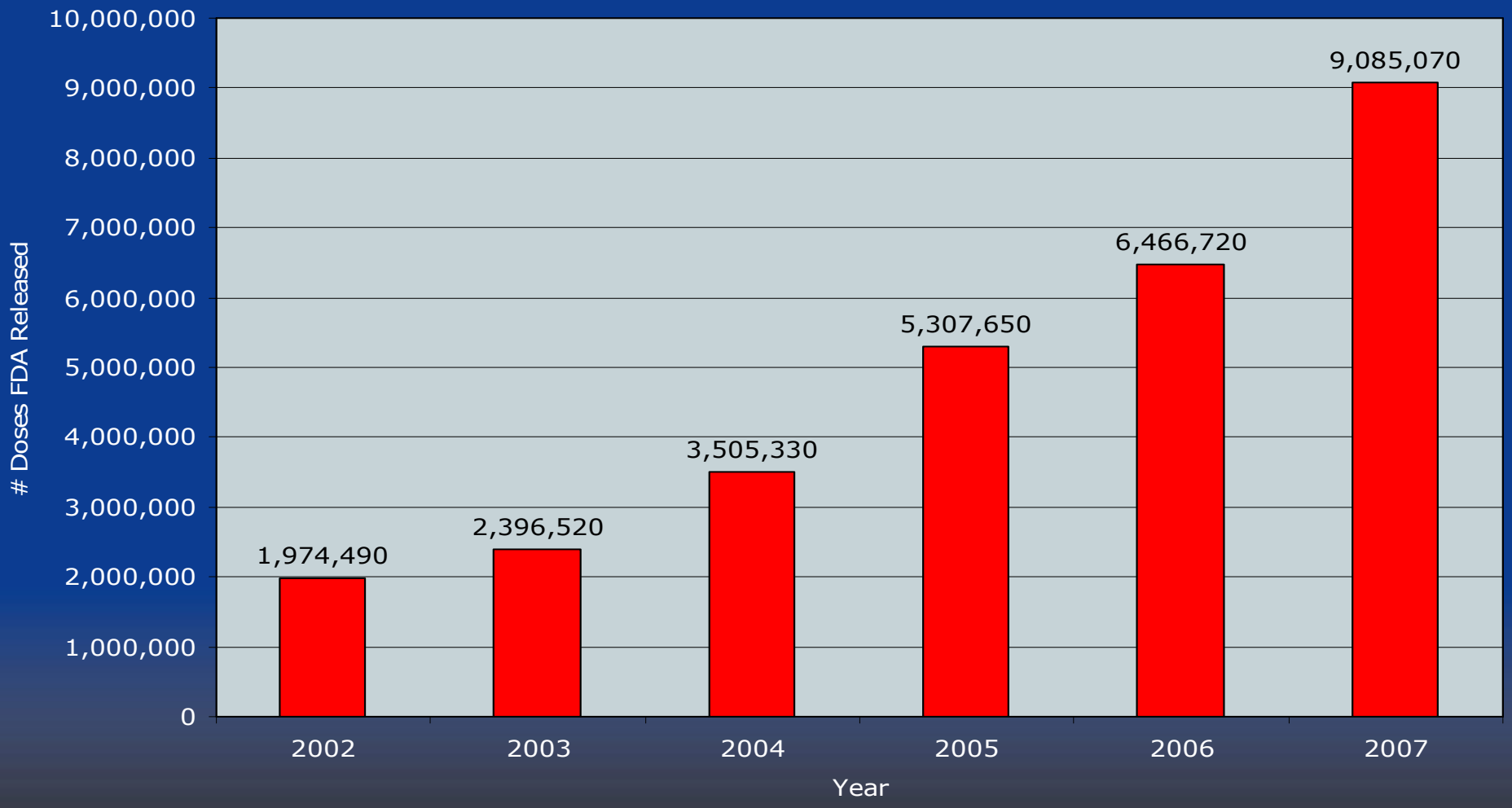
1 *Federal Register* 1985; 50:51002
2 IOM report, 2002
3 Marano, et al. JAMA 2008

Issues Considered
Pre-event Administration

	+/-
Burden of Disease	-/+
Risk of exposure	+/-
Safety	+
Efficacy	+
Supply	

+ Favors pre-event vaccine
- Does not favor pre-event vaccine

AVA Dose Availability



Courtesy Dr. Waytes
Emergent BioSolutions

Current and Future AVA Supply

- Single manufacturer
- Since 2002…
  - Renovated, FDA approved manufacturing facility
  - Improved production processes and quality systems
- Current capacity 8-9 million doses per year
- Future annual production capacity could reach 30-35 million doses
- Commercially available

Courtesy Dr. Waytes
Emergent BioSolutions

Issues Considered
Pre-event Administration

	+/-
Burden of Disease	-/+
Risk of exposure	+/-
Safety	+
Efficacy	+
Supply	+

+ Favors pre-event vaccine
- Does not favor pre-event vaccine

Work Group Draft Recommendations for Pre-Exposure/Pre-Event Use of AVA

Persons at Risk, Pre-event

- General Public
  - General Public/Medical Personnel
  - Pregnant/Breastfeeding Women
  - Pediatric Populations
- Occupational Exposures
  - Persons Handling Animals/Animal Products
  - Laboratorians
  - Postal Processing Facilities
  - Military Personnel
- Response Efforts
  - Environmental Investigators/Remediation Workers
  - Emergency and Other Responders

Pre-Event Vaccination
General Public

Population	*2000*	*2008, Draft*
General Population (pg 36)	Not Recommended	Not Recommended
Pregnant Women	Not well addressed	Discussed later
Breastfeeding Women	Not well addressed	Discussed later
Pediatric Populations (pg 36)	Not addressed	Not Recommended

Pre-Exposure Vaccination
Occupational Exposures

Population	*2000*	*2008 Draft*
Animals/Animal Product Handlers (pg 37)	Only for persons for whom industry standards are insufficient; in areas of high incidence	Only for persons for whom industry standards are insufficient; in areas of high incidence
Laboratorians (pg 37)	Working with cultures; activities with potential for aerosol production	Only for persons at risk for repeated exposure to *B. anthracis* spores

Pre-Event Vaccination
Occupational Exposures

Population	*2000*	*2008 Draft*
Postal Processing Facilities (pg 37)	**Not addressed**	**Not recommended due to presence of biodetection systems**
Military (pg 37)	**If calculable risk assessed, may be indicated**	**Recommended if Dept of Defense determines calculable risk of exposure to aerosolized *B. anthracis* spores**

Pre-Exposure Vaccination
Response Efforts

Population	*2000*	*2008 Draft*
Persons with Repeated Exposures (i.e., remediation) (pg 37)	Recommended "…other groups for whom a calculable risk could be assessed…"	Recommended

Emergency and Other Responders

- Draft statement defines as "…include, but not limited to, police departments, fire departments, hazardous material units, government responders, and the National Guard…"
- Not recommended in 2000
- Not recommended in 2002 due to vaccine supply
- Draft language presented to ACIP in June 2008

Emergency and Other Responders
Option 1

Occupational groups <as defined on page 15> who may be engaged in response activities in areas with of *B. anthracis* spore contamination (e.g., site investigation, building evacuation, maintenance of critical infrastructure, suspicious substance/"white powder" incidents) and therefore may be exposed to aerosolized *B. anthracis* spores, but for whom a calculated risk assessment does not exist, may consider pre-event vaccination on a voluntary basis and under the direction of a comprehensive occupational health and safety program.

Emergency and Other Responders
Option 2

Occupational groups engaged in response activities <as defined on page 15> are not routinely recommended to receive anthrax vaccine due to lack of a calculable risk assessment. However, selected groups with potential engagement in response activities that may lead to exposure to aerosolized *B. anthracis* spores may choose to offer their workers pre-event vaccination on a voluntary basis and under the direction of a comprehensive occupational health and safety program.

Discussion/Vote

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Pre-Exposure Vaccination
Delayed Doses

- Anti-PA IgG response in 279 DoD personnel
  - Served in Operations Desert Storm and Desert Shield
  - Received 1, 2, or 3 doses AVA; last dose 18-24 months before study
- Tested initial titers, provided next dose, measured Anti-PA IgG response 1 month later
- Robust immune response
  - 99.3% had measurable anti-PA Ab in 1-month follow-up sera
  - Overall GMT increased 139-fold
  - Lowest GMT increase 78-fold increase (dose 2 recipients)
- No negative safety findings

Pittman, et al. Antibody response to a delayed booster dose of anthrax vaccine and botulimun toxoid. Vaccine 20 (2002) 2107-2115.

Pre-Exposure Vaccination
Delayed Doses
WG Recommendation

Available AVA specific data suggests that increasing the interval between doses does not adversely affect the ultimate serologic response achieved, nor post-vaccination safety. Therefore, as with other vaccines, interruption of the vaccination schedule does not require restarting the entire series or the addition of extra doses.

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Post-Exposure Prophylaxis (PEP)

- To prevent inhalation anthrax development
  - For persons with high likelihood of exposure to aerosolized *B. anthracis* spores
- Currently 3 doses of AVA (0, 2, 4 weeks) + antimicrobials
  - AVA administered under an IND* or EUA**

*Investigational New Drug application
**Emergency Use Authorization

Previous ACIP recommendations

- 2000
  - Antibiotic therapy should be continued for at least 30 days and longer antibiotic therapy (up to 42-60 days) might be indicated
  - If available, provide vaccine (0,2,4 weeks); discontinue antimicrobials after the 3rd dose
- 2002
  - ACIP endorsed 3-doses of vaccine (0, 2, 4 weeks) in combination with antimicrobials
    - Might be prudent to continue antimicrobials 14 days past 3rd dose of vaccine
  - 60 days of antimicrobials if no vaccine

PEP 2000/2002

- Antimicrobial duration language confusing
- Need concise recommendations
  - Target groups
  - Duration of antimicrobial use

Issues Considered

- Safety and Effectiveness of Vaccine
- Safety and Effectiveness of Antimicrobials
- Effectiveness of Combination

Data to Support Post-Exposure Use of Anthrax Vaccine

- Non-human primate studies suggest inhaled *B. anthracis* spores may persist up to 100 days*
- Antibody titers peak 10-14 days following 3rd dose of vaccine**
  - Provides benefits following discontinuation of antimicrobial agents

*Henderson, 1956

Data to Support 60 Days Post-exposure Use of Antimicrobials

- Inhalation anthrax incubation periods 1-43 days*
  - Antibody titers peak 10-14 days after 3rd dose
  - Require protection before titers peak

*Brachman 1980;
Meselson M, 1994

Antimicrobial Agents Utilized Post-exposure

- FDA indication “60 days”
  - Ciprofloxacin
  - Doxycycline
  - Levofloxacin
- Only used under IND/EUA
  - Amoxicillin (if MIC $\leq$ 0.125 mcg/mL)

PEP Antimicrobial Agents
2001 BT Event

- **Safety**
  - Similar AEs reported after 30 days between cipro and doxy
  - Most AEs mild
  - Unable to assess impact of stress, anxiety, enhanced symptom awareness
- **Adherence**
  - 44% (range: 21-64%) adherence
  - Risk perception was stronger predictor of adherence than AEs

*Shepard, ** Tierney, *** Martin

Efficacy of AVA with Antimicrobials

- No human studies
- Limited NHP studies
- WG reviewed 1993 study*
  - All animals receiving AVA + antimicrobials survived following antimicrobial discontinuation

*Friedlander AM, et al. J Infect Dis 1993; 167:1239-43

WG Conclusion, PEP

- Vaccination maximizes protection with:
  - Imperfect adherence to antimicrobials
  - Long term spore germination and outgrowth
- Antimicrobial agents provide protection for the duration of their use
- Unvaccinated persons need both to provide protection following exposure

Work Group Draft Recommendations for Post Exposure Prophylaxis Use of Vaccine

Post-exposure Prophylaxis

I. Previously unvaccinated persons following any inhalation exposure
II. Pediatric populations
III. Previously vaccinated persons with repeated occupational exposures

    (Remediation Workers/Environmental Investigators)
IV. Pregnant/Breastfeeding women

I. Post-Exposure Prophylaxis Following Any Inhalation Exposure: Previously Unvaccinated Persons

- 60 days of appropriate antimicrobial prophylaxis combined with 3 doses of AVA is the best available protection against inhalation anthrax
- Vaccine should be offered within 10 days of the exposure
- Peak serologic response occurs within 10-14 days following the 3rd dose of anthrax vaccine. To prevent a lapse in protection, persons for whom vaccination was delayed should extend antimicrobial use to 10-14 days after the 3rd dose, even though this practice may extend antimicrobial use past 60 days.

II. Post-Exposure Prophylaxis
Pediatric Populations

- Anthrax vaccine is not licensed for use in pediatric populations and has not been studied in children. The use of AVA in pediatric populations in a post-event setting with a high risk of exposure to aerosolized *B anthracis* spores is not contraindicated; however, its use is considered a precaution. The risks and benefits of using post-exposure vaccination in children will be considered based on the specific circumstances of an event and exposure prior to making a recommendation on use of AVA in children. Antimicrobial agents should be employed, as described above in Antimicrobial Considerations for Pediatric Use.

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Post-exposure Prophylaxis

I. Previously unvaccinated persons following any inhalation exposure
II. Pediatric populations
III. Previously vaccinated persons with repeated occupational exposures

    (Remediation Workers/Environmental Investigators)
IV. Pregnant/Breastfeeding women

Previous ACIP recommendations

- 2000
  - Partially/Fully vaccinated persons not separately addressed
- 2002
  - Partially/Fully vaccinated persons receive at least 30-day course of antimicrobial PEP; continue licensed vaccine regimen.
  - Antimicrobial PEP not needed for vaccinated persons in Biosafety Level 3 laboratories under recommended conditions nor (fully) vaccinated persons wearing appropriate personal protective equipment (PPE) while working in contaminated environments…unless respiratory protection disrupted

Worker PEP
2001 BT Event

- ACIP guidance interpreted as “following last exposure”
- Low threshold for “PPE disruption”
- Some workers on antimicrobials >12 months

Issues Considered
Repeated Occupational Exposures

	+/-
Safety/Effectiveness of vaccine	+
Safety/Effectiveness of antimicrobials	+
Safety/Effectiveness of antimicrobials - long term	
Effectiveness of PPE	

+ Acceptable
- Not acceptable

Long Term Use of Antimicrobials for PEP

- Civilian adherence 44% (range 21%-64%) in 2001
  - No data on adherence among remediation workers (longer duration abx)
- Limited data on safety of long term (>28 days) levofloxacin use
- Risk of tendinitis/tendon tears with quinolone use*

*http://www.fda.gov/cder/drug/InfoSheets/HCP/fluoroquinolonesHCP.htm

Issues Considered
Repeated Occupational Exposures

	+/-
Safety/Effectiveness of vaccine	+
Safety/Effectiveness of antimicrobials	+
Safety/Effectiveness of antimicrobials - long term	?
Effectiveness of PPE	

+ Acceptable
- Not acceptable

Personal Protective Equipment (PPE)

- Defined as "powered air-purifying respirator with full-facepiece and high-efficiency particulate air (HEPA) filters, disposable protective clothing with integral hood and booties, and disposable gloves"*
- Protective if properly selected, assembled, and fitted
- Last line of defense in the hierarchy of controls
  - Individual work practices might lead to exposure
  - Breaches in environmental controls might occur
  - Some breaches may go unrecognized

http://emergency.cdc.gov/agent/anthrax/environment/investigatorppe.asp

Issues Considered
Repeated Occupational Exposures

	+/-
Safety/Effectiveness of vaccine	+
Safety/Effectiveness of antimicrobials	+
Safety/Effectiveness of antimicrobials - long term	?
Effectiveness of PPE	+*

*if properly selected, assembled, and fitted

+ Acceptable
- Not acceptable

Post-Exposure Prophylaxis
Repeated Occupational Exposures

Population	*2000*	*2008 Draft*
Fully Vaccinated + PPE	No Abx PEP	No Abx PEP*
Partially Vaccinated	30+ day course; continue vaccine	30 days Abx PEP; continue vaccine
Fully Vaccinated; no PPE	Implied: 30+ day course; continue vaccine	30 days Abx PEP; continue vaccine

*may seek additional protection through occupational health services

Post-Exposure Prophylaxis
Repeated Occupational Exposures

Population	*2000*	*2008 Draft*
Fully Vaccinated; PPE breached	30+ day course; continue vaccine	30 days Abx PEP; continue vaccine
No previous vaccine	Not addressed	60 days Abx PEP; begin vaccination

Repeated Occupational Exposures

- ACIP believes that the combination of vaccine and appropriate PPE provides effective protection for fully vaccinated persons working in occupations with repeated exposure to potentially aerosolized *B. anthracis* spores. Antimicrobial PEP is therefore not needed for fully vaccinated workers wearing appropriate PPE while working in environments contaminated with *B. anthracis* spores unless their PPE is disrupted.
- A 30 day course of antimicrobial PEP is recommended for partially vaccinated workers, fully vaccinated workers wearing no PPE, and fully vaccinated workers for whom PPE is disrupted; these workers should also continue with their licensed vaccination regimen. A 60 day course of antimicrobial PEP, along with starting the licensed regimen, is recommended for previously unvaccinated workers. Fully vaccinated workers who desire additional protection may consider antimicrobial PEP under the direction of their occupational health program.

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