Draft Recommendations for the Pre-Event Use of Anthrax Vaccine Among First Responders

Options for Consideration

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On behalf of the
Anthrax Vaccine Work Group

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Anthrax Vaccine Adsorbed

- Pre-event
  - To immunize at-risk persons prior to aerosolized exposure/event
- Post-event
  - Utilized in a post bioterror setting
  - 3 doses plus antimicrobial agent

ACIP 2000 Recommendations
Pre-Event Vaccination

- **Routine vaccination with AVA indicated for persons engaged in work or activities:**
  - **Involving production quantities or concentrations of *B. anthracis* cultures with a high potential for aerosol production**
  - **With imported animal hides, wool, only when workplace practices are inadequate**
- **Persons not at increased risk and therefore not recommended to routinely receive pre-event vaccination**
  - **BSL-2 laboratorians routinely processing clinical samples**
  - **Veterinarians in the US**
    - **Might be indicated in areas with high incidence of anthrax**

*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 2000 Recommendations
"Bioterrorism Preparedness"

- "Although groups initially considered for pre-exposure vaccination for bioterrorism preparedness included emergency first responders, federal responders, medical practitioners and private citizens, vaccination of these groups is not recommended"
- Recommendations should be based upon a calculable risk assessment
  - The target population at risk cannot be predetermined
  - The risk of exposure cannot be calculated
  - Extremely low risk for exposure due to secondary aerosolization
  - For groups for whom a calculable risk can be quantified, vaccination may be indicated

*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.

2002 ACIP
Pre-Event Recommendations

- Amid "…concerns that the current anthrax vaccine supply is limited …" and because "In December 2001, the U.S. Department of Health and Human Services obtained a limited supply of anthrax vaccine …"
- "ACIP recommends that groups at risk for repeated exposures should be given priority for pre-exposure vaccination"
  - Specific laboratory personnel
  - Workers who 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.

Current Pre-Event Regimen (2000/2002)

- Approved FDA licensed regimen
  - 6 dose priming series over 18 months
  - Subcutaneous administration
  - Annual boosters
  - ACIP recommended the use of antimicrobial agents following exposure for at least 30 days*
    - For partially or fully vaccinated persons
    - Partially vaccinated persons recommended to continue vaccination course along with antimicrobials

*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.

Potential Schedule Changes

- FDA reviewing Biologics License Change Application (BLA)
  - Drop 2 week dose
  - Alter route of administration to IM
- Possible ruling this fall

Current Pre-Event Vaccination Programs

- Limited
  - Previous laboratorian program discontinued
- Vaccine is commercially available
  - Vaccination through private practitioners rare

Current Issue
First Responder Organizations

- Some first responder groups requesting
  - Clarification of supply language
  - Specific recommendation for vaccination
- Complicating Factors
  - No single representative organization
  - Multiple types of “first responders”
  - Programmatic issues are complex

Issues Considered
Pre-event AVA administration

	+/-
Safety	
Efficacy	
Supply	
Programmatic	

+ evidence sufficient to recommend
- evidence not sufficient to recommend

Safety

- Published reviews conclude the vaccine is at least reasonably 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
- Potential for rare AEs

*references on slide 32

AVA 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	1 - 8	1 - 36	3 - 42	67 - 83

*IOM report, 2002
Slide courtesy of Col Cieslak

VAERS and AVA*

- AVA accounts for
  - ~44% of reports filed by military
    - 61.1 reports/100,000 doses
  - Parallels anthrax vaccine program starts and stops
- Military associated reports through June 2008
  - 4705 (44.2%)
  - ~10% “serious” adverse events
- VAERS does not establish causality

*courtesy VAERs/Susan Duderstadt

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Brachman Study, 1962

- Combined Efficacy: 92.5% (95% CI: 65-100%)
- 26 cases of anthrax
  - 21cutaneous:
    - 19 in unvaccinated persons
      - Placebos/refusals/persons not thought to be at risk
    - 2 among incompletely vaccinated persons
  - Inhalation anthrax:
    - 0 cases among vaccinated persons
    - 5 cases (4 fatal) in unvaccinated persons
      - Placebos/refusals

Am J Public Health 1962;52:632

CDC Data*

- Collected from 1962-1974
  - Reviewed by FDA in 1985
- 6986 persons received ~16,500 doses
- 27 cases of anthrax
  - All in unvaccinated/partially vaccinated persons
- "…no cases have occurred in fully vaccinated subjects while the risk of infection has continued. These observations lend further support to the effectiveness of the product."
- "…believes that there is sufficient evidence to conclude that anthrax vaccine is safe and effective…"

Federal Register 1985; 50:51002

Efficacy of AVA

- **Human efficacy studies**
  - **Brachman, *Am J Public Health* 1962;52:632**
  - **CDC Observational Study, pub 1985**
  - **Anthrax Vaccine Research Program ongoing dose reduction/route change study**
    - **Potential correlate of protection**

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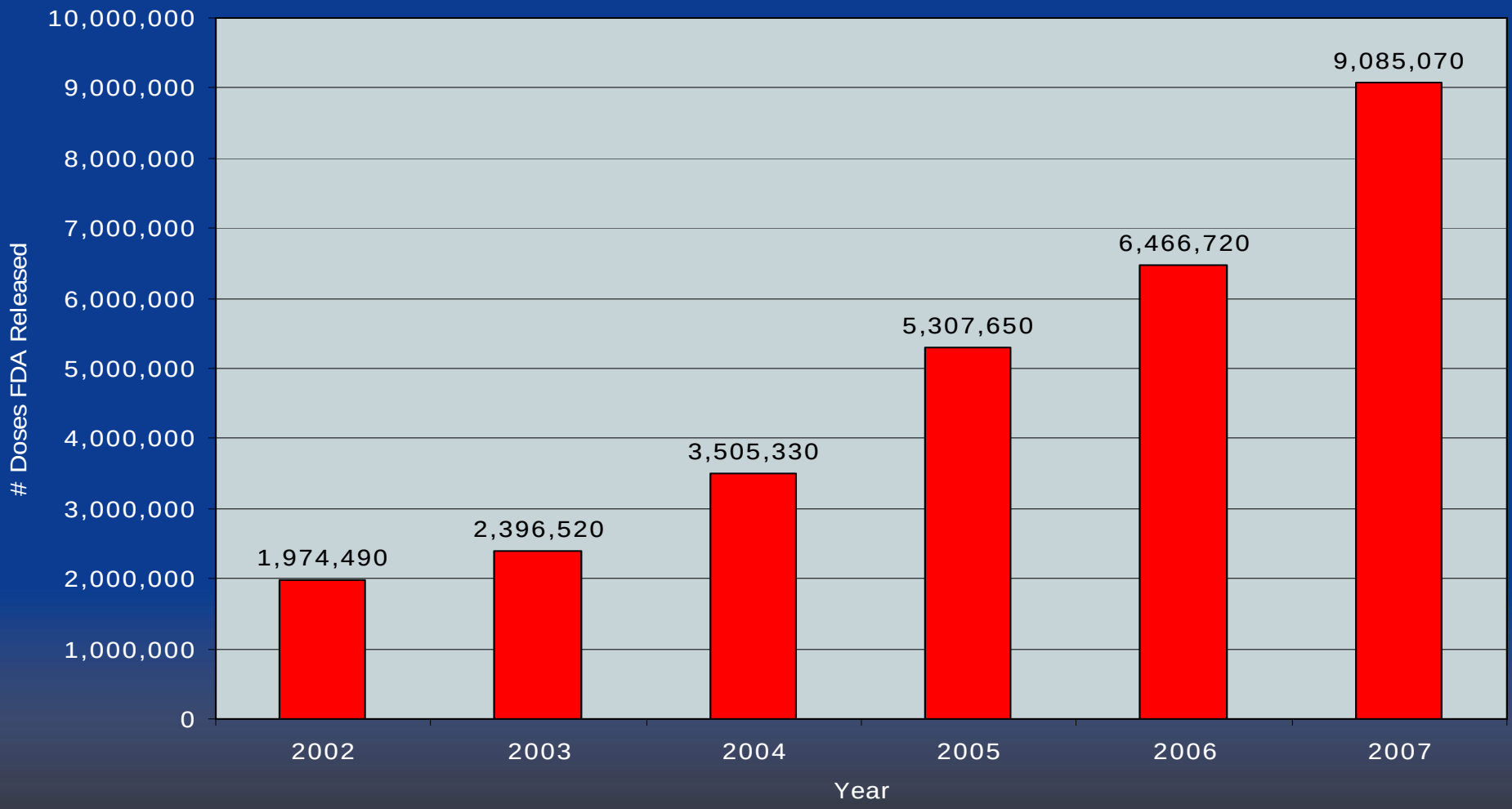
Dose Availability



Courtesy Dr. Waytes
BioThrax Manufacturing Overview

Current and Future Supply

- Since 2002…
  - Renovated manufacturing facility
  - Improved production processes and quality systems
  - FDA Final Order issued
- Current annual production capacity is 8-9 million doses
- Future annual production capacity could reach 30-35 million doses
- Commercially available

Courtesy Dr. Waytes
BioThrax Manufacturing Overview

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Programmatic

- Schedule
- Risk versus benefit
- Responsibility for campaign
- Responsibility for post-vaccination surveillance
- Impact on preparedness

Complicated Schedule

- 6 priming doses over 18 months
- Annual boosters
- Tracking of personnel

Risk-Benefit

- Risk-benefit analysis
  - National, single analysis
    - Varies by First Responder subgroup, location
    - Must define “First Responder”
    - Adverse events can occur
- Risk assessment
    - Requires classified knowledge
    - Evolving
    - Must be at the local level
- Perception of risk varies

Vaccination Campaign Responsibilities

- Local, state, federal, responder organization itself, private providers/insurance
- Provide education to vaccinees
- Maintain campaign
  - New entrants/annual boosters
  - Sustainability of funding
- Liability coverage

Post-Vaccination Activities

- Local, state, federal, responder organization itself, private providers/insurance
- Monitor for adverse events
  - Report AEs as necessary
  - VAERS forms
- Provide care in event of serious adverse event
- Worker's compensation/liability programs

Impact of Pre-event Vaccination on Preparedness

- Will offer additional protection beyond vaccination at the time of the event
  - Early priming of immune system - added benefit especially to persons exposed to large inoculums
- May support a more rapid and willing community of emergency responders

Impact of Pre-event Vaccination on Preparedness
Post-exposure Antimicrobial Use

- Per current recommendations, continued need for antimicrobials post exposure
- Pre-event vaccine beneficial in the events:
  - Public health infrastructure cannot ensure availability or timely delivery of antimicrobial PEP
  - Attack strain bio-engineered for resistance against PEP antimicrobial agents
  - Covert exposure/release

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Pre-event AVA administration

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Efficacy	+
Supply	+
Programmatic	+/-

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Recommendations
Options for Consideration

- Remove supply language
- WG discussed 4 options

1. “not recommended” – the current language
2. “may consider”
3. “should be encouraged”
4. “recommended”

WG recommendation

- **"Groups for whom potential contact with aerosolized anthrax is a reasonable expectation based on occupation and duties (e.g. first responders expected to be called to the scene of a bioterrorist event) and for whom a calculable risk is not available may consider pre-event vaccination on the basis of an estimated risk benefit and in the context of an occupational health and safety program."**

Discussion

Future Activities

- Refine this recommendation

- Draft post-exposure prophylaxis recommendations
- Draft recommendation around missed doses
- Revise statement
- Present statement and new recommendations for a vote in October

Independent Scientific Reviews (since 1985)

- FDA Advisory Panel on Bacterial Vaccines and Toxoids
  - *Federal Register*, 1985
- Defense Health Board (DHB)
  - advisory group to DoD, 1994-present
- Cochrane Collaboration, Oxford
  - *Vaccine*, 1998, 2004
- Working Group on Civilian Biodefense
  - *JAMA*, 1999, 2002
- CDC's Advisory Committee on Immunization Practices
  - *MMWR*, 2000
- Anthrax Vaccine Expert Committee (AVEC)
  - *Pharmacoepidemiology and Drug Safety* , 2002, 2004
- National Academy of Sciences (IOM), 2002
- FDA Review of VAERS reports
  - supports FDA's Final Rule and Final Order, 2005