Updating Recommendations for Use of Anthrax Vaccine in the United States

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Agenda

- **Background**
  - Anthrax
  - Anthrax Vaccine Adsorbed (AVA)
  - Anthrax antitoxin
  - 2010 AVA ACIP recommendations
  - Anthrax antitoxin for postexposure prophylaxis
- **Reconvening ACIP workgroup**
  - New/reanalyzed data
  - Reformulation of AVA
  - Terms of Reference
  - Workgroup Members

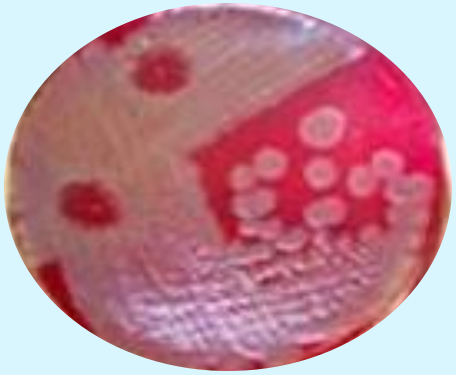
BACKGROUND ON ANTHRAX

ACIP Meeting
June 20/28, 2017

National Center for Emerging and Zoonotic Infectious Diseases
Division of High-Consequence Pathogens and Pathology

The Agent

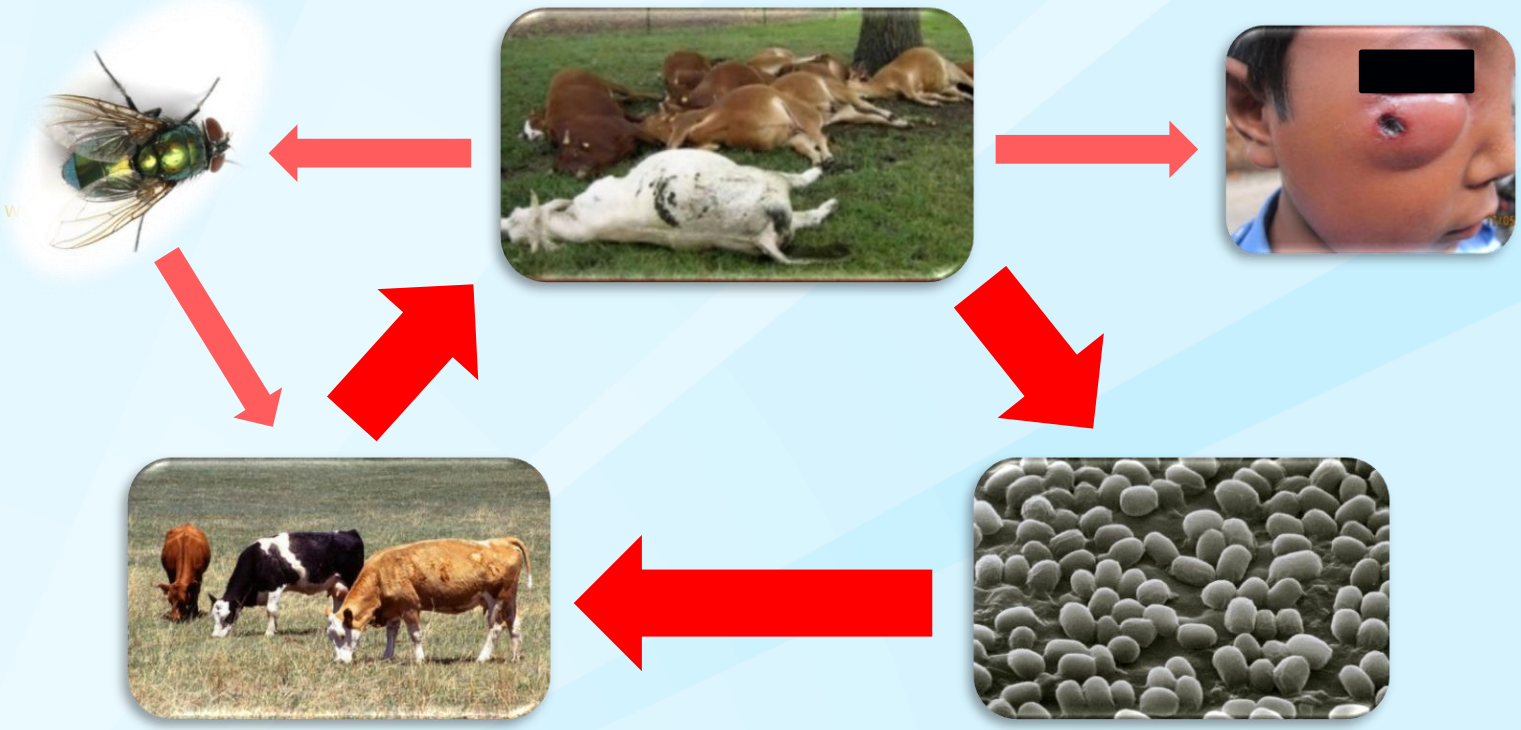
- ***Bacillus anthracis*** **is the causative agent of anthrax**
  - Gram positive spore-forming bacterium
- **Spores are the infective form**
  - Can be mass produced and released as an aerosol as a bioweapon
- **Vegetative form produces two major toxins**



Epidemiology: Naturally Occurring Disease

- **Primarily disease of herbivores that ingest spores**
- **Human contact with infected animals/animal products**
  - Woolsorter's disease
- **Butchering and eating of contaminated carcasses**
  - Both cutaneous and gastrointestinal cases
- **Incidental inhalation of spores from work or hobby**
  - Drummer cases

Cycle of *B. anthracis* Infection



Adapted from: Turnbull PC. Anthrax in humans and animals. 4th ed. Geneva, Switzerland: World Health Organization; 2008.
Images: CDC Public Health Image Library www.phil.cdc.gov unless otherwise noted

Types of Anthrax

- Cutaneous
- Ingestion
- Inhalation
- Injection
- Meningitis

Cutaneous Anthrax

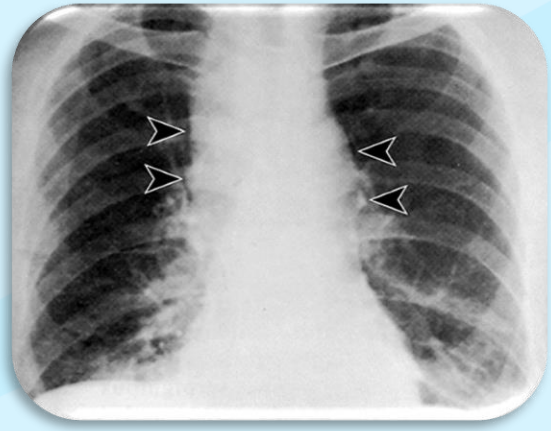
- **Most common form**
- **Transmission:** spores introduced through skin (often, but not always through pre-existing abrasions)
- **Germination:** 1-3 hours after inoculation
- **Incubation:** 1-17 days
- **Case fatality rate:**
  - Without treatment: ~24%
  - With antimicrobial treatment: <2%

Ingestion Anthrax

- **2nd most common form of naturally occurring anthrax**
- **Transmission:** ingestion – unclear whether it is spores or vegetative cells in poorly cooked meat
- **Two forms:** oropharyngeal and abdominal
- **Incubation:** 1- 14 days
- **Case fatality rate with treatment:** 40%; but may be higher in children

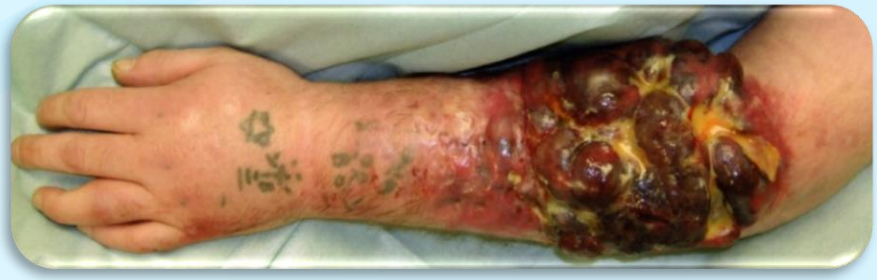
Inhalation Anthrax

- **Transmission:** inhalation of aerosolized spores from hair/hides/animals or BW- or BT-related events
- **Incubation:**
  - Range in humans: 1-43 days
  - Sverdlovsk: 2-43 days
  - 2001: 5-13 days
- **Case fatality rate with treatment**
  - 1900-2000: 92%
  - 2001 and after: 47%



Injection Anthrax

- **Recently identified in heroin-injecting drug users in northern Europe**
  - These are severe soft tissue infections that are deep under the skin or in the muscle where the drug was injected.
  - Never reported in the United States.
- **Transmission:** injection of contaminated heroin, though the mode of abuse was not well documented in most reports
- **Incubation:** 2-10 days
- **Case fatality rate with treatment:** 37%

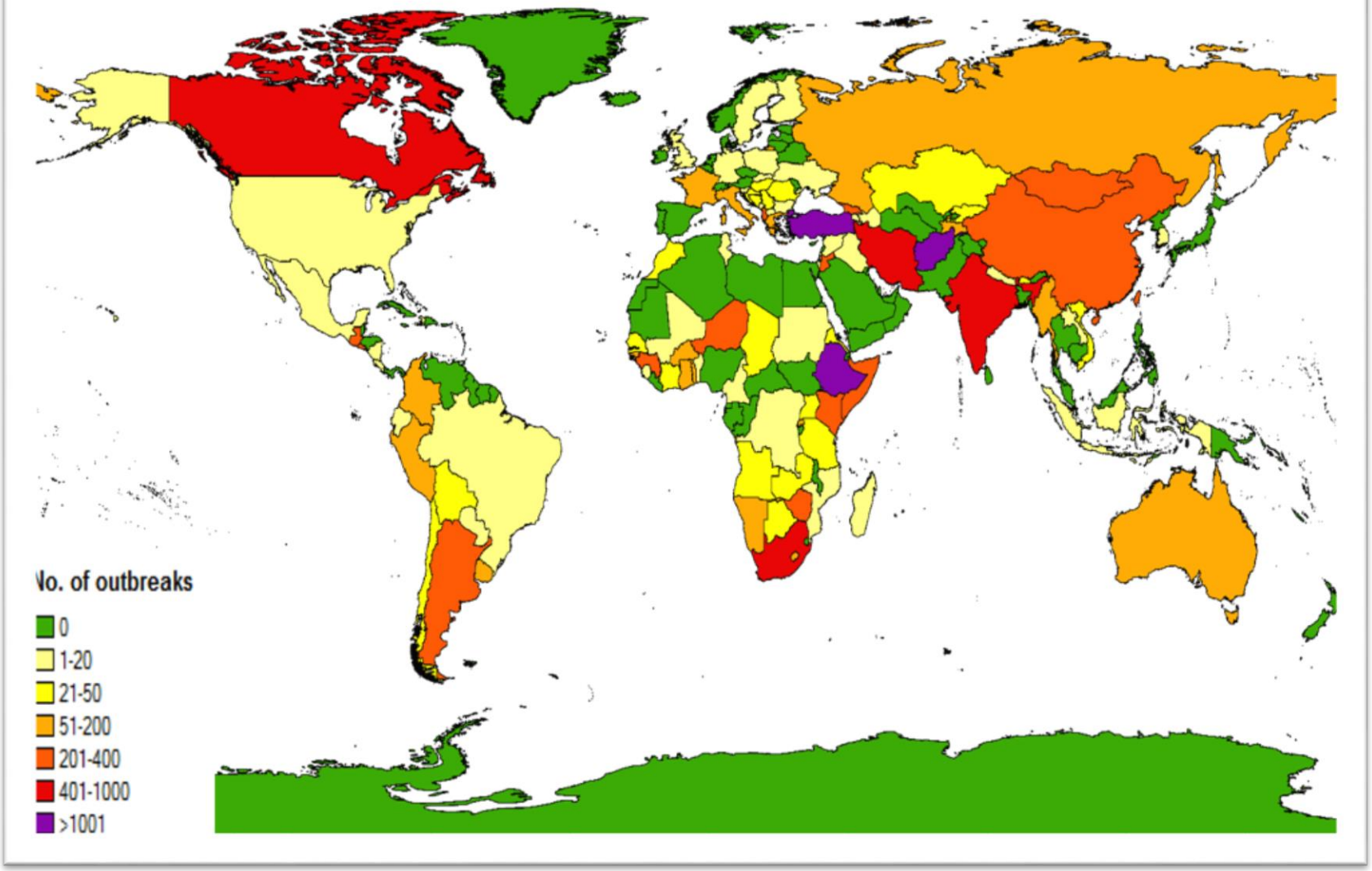


Meningitis

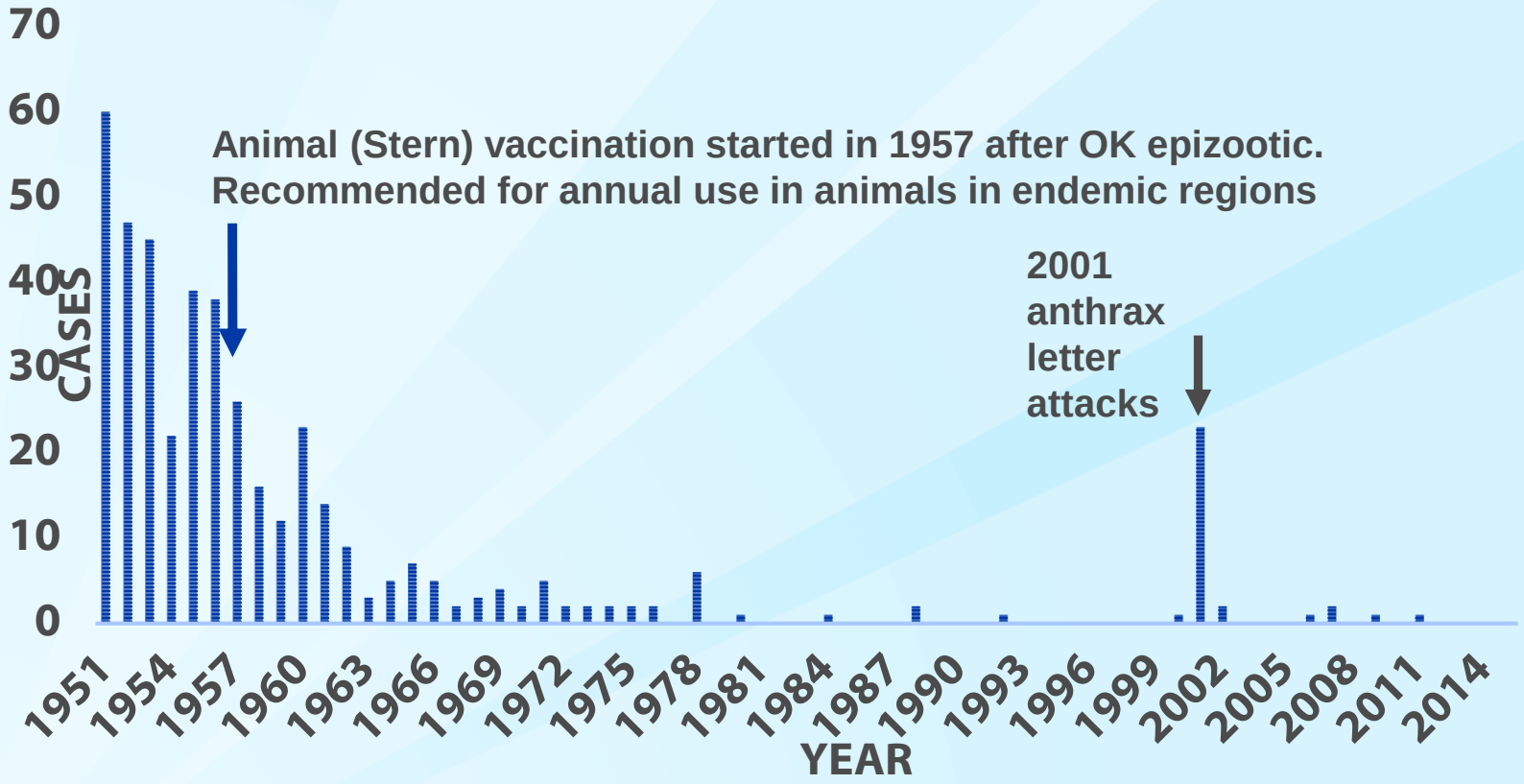
- **Can accompany inhalation, ingestion, cutaneous, or injection disease**
  - 21/38 (55%) brains examined at autopsy in Sverdlovsk had hemorrhagic meningitis[1]
- **Can occur as a primary manifestation of anthrax (i.e., no other route of transmission)[2]**
- **Case fatality rate for meningitis secondary to inhalation anthrax, 1900 – 2005[3]:**
  - 100% (30/30) with meningitis died
  - 81% (42/52) without meningitis

1. Abramova FA. *Proc Natl Acad Sci.* 1993;90:2291-94
2. Holty JE. *Ann Emergency Med*. 2006;200-211.
3. Holty JE. *Ann Int Med.* 2006;144:270-80.

Global Distribution of Anthrax, 2005- 2016



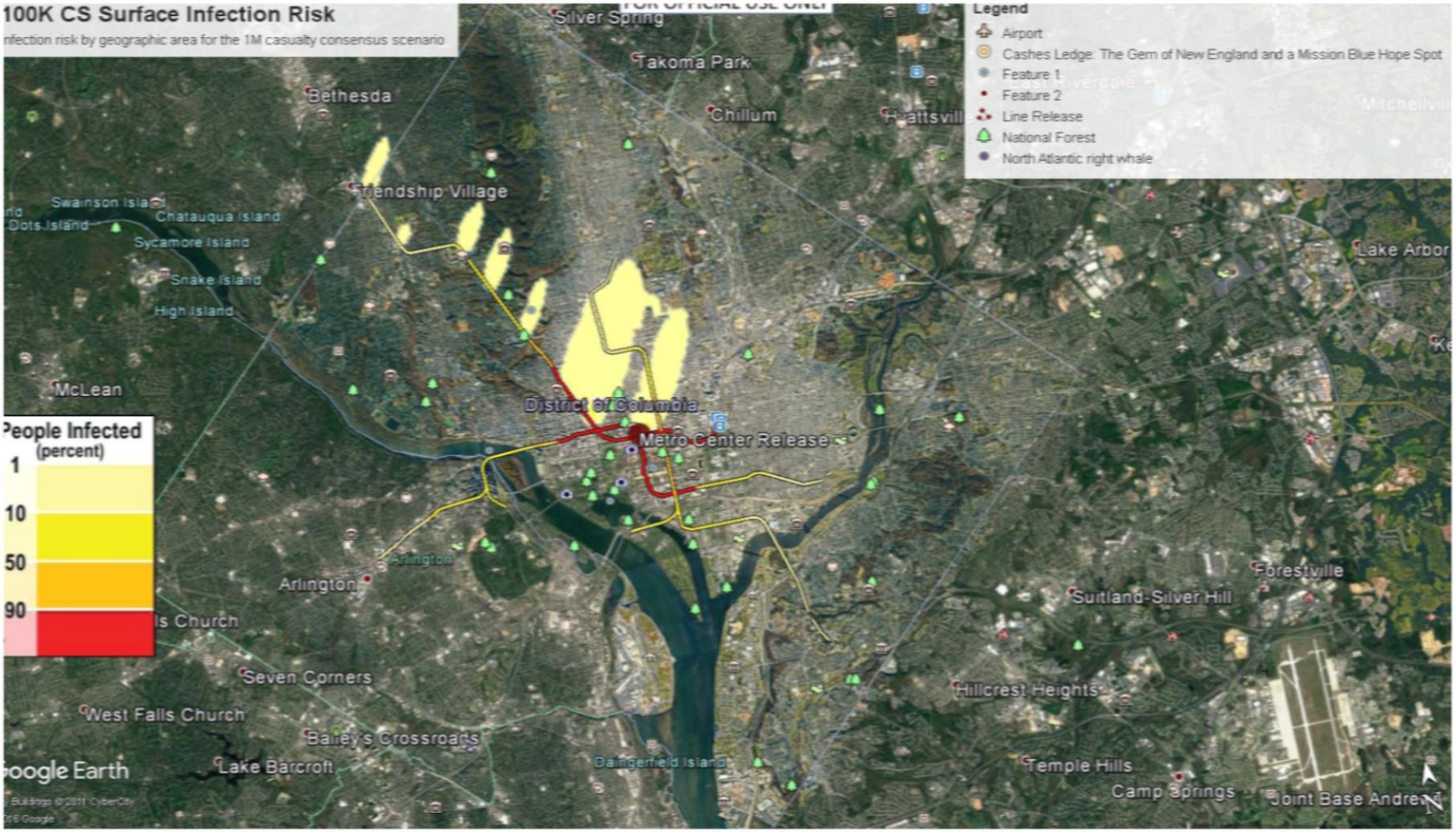
Cases of Human Anthrax in U.S., 1951–2014 (N = 439)



Epidemiology: Bioterrorism

- **Anthrax spores:** the most likely bioweapon
  - Relatively easy and cheap to produce
  - Can be stored for a long time
  - Can be aerially dispersed a variety of ways
  - Odorless, colorless, tasteless
  - Inhalation anthrax is highly lethal
  - May survive > 40 yrs
- **Can cause widespread illness and death among unprotected persons**
  - Sverdlosk incident, 1979
  - US mail incident, 2001

Hypothetical Wide Area Outdoor Release



BACKGROUND ON AVA

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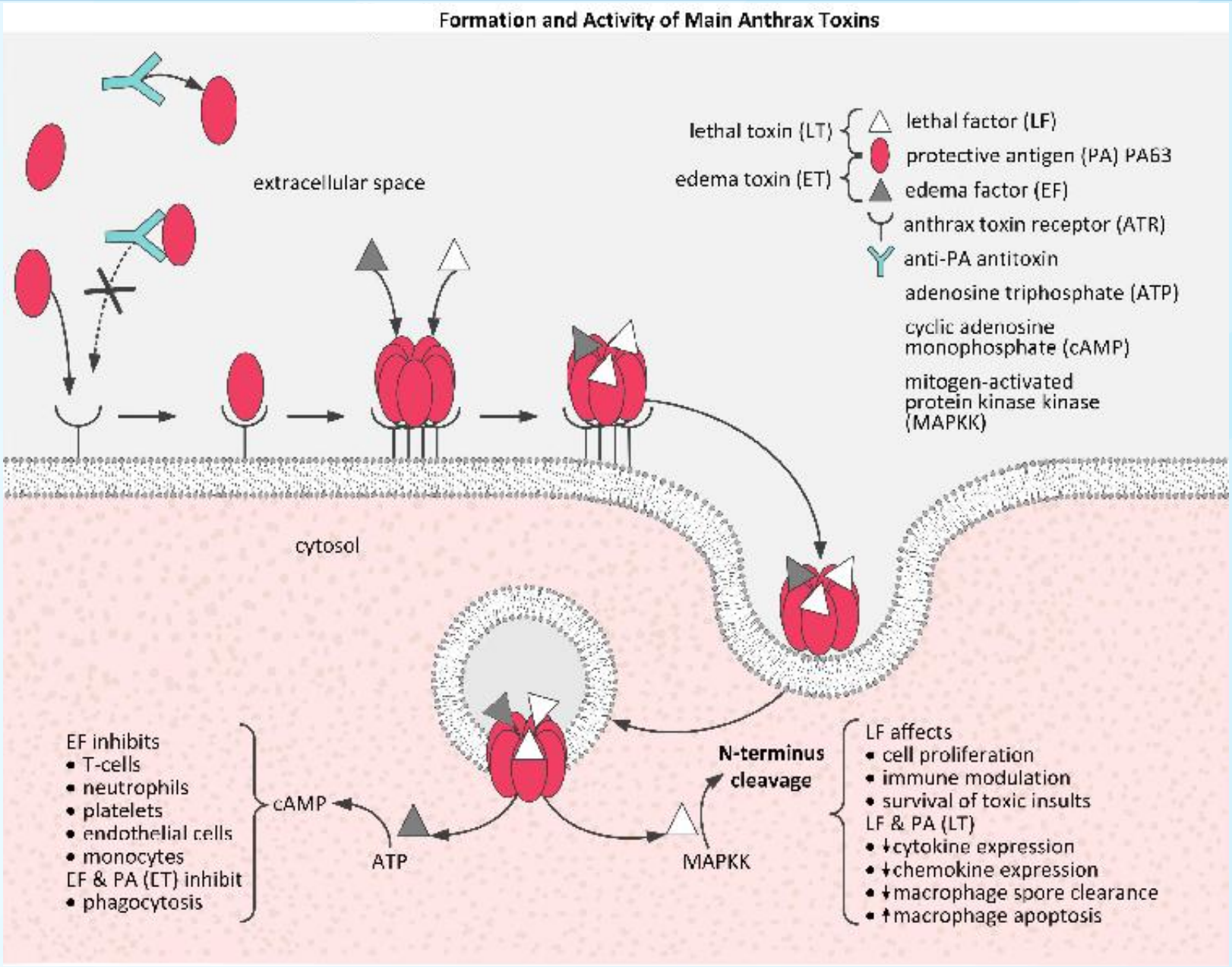
Anthrax Vaccine Facts

- **Anthrax Vaccine Adsorbed (BioThrax®)**
  - Manufactured
    - Michigan Dept of Health until 1998
    - Currently Emergent BioSolutions
  - Aluminum hydroxide precipitate
  - Sterile, cell-free filtrate made from microaerophilic cultures of avirulent, non-encapsulated *B. anthracis**
- **Final product***
  - Adjuvant: 1.2 mg/mL aluminum
  - Preservatives: 25 µg/mL benzethonium chloride and 100 µg/mL formaldehyde

* http://www.biothrax.com/


Formation and Activity of Main Anthrax Toxins
extracellular space
lethal toxin (LT)
edema toxin (ET)
lethal factor (LF)
protective antigen (PA) PA63
edema factor (EF)
anthrax toxin receptor (ATR)
anti-PA antitoxin
adenosine triphosphate (ATP)
cyclic adenosine monophosphate (cAMP)
mitogen-activated protein kinase kinase (MAPKK)
cytosol
EF inhibits
• T-cells
• neutrophils
• platelets
• endothelial cells
• monocytes
EF & PA (ET) inhibit
• phagocytosis
cAMP
ATP
N-terminus cleavage
MAPKK
LF affects
• cell proliferation
• immune modulation
• survival of toxic insults
LF & PA (LT)
• ↓cytokine expression
• ↓chemokine expression
• ↓macrophage spore clearance
• ↑macrophage apoptosis

Anthrax Vaccine Adsorbed

- **Vaccine primes immune system**
  - To recognize and block protective antigen (PA)
  - PA is common to all anthrax strains
  - Vaccine efficacy demonstrated against numerous anthrax strains in various animal studies

Anthrax Vaccine History

- **1950s: Ft. Detrick/"Merck" formulation**
  - Cell culture filtrate; precipitated with alum
  - Brachman studies
    - Brachman et al. Am J Pub Hlth 1962;52:632.
- **1960s: "Lansing" formulation**
  - Manufacturing process improved
  - Increased PA concentration, purity, and potency
- **1970s: "Lansing" formulation licensed**
  - Used data from Brachman studies ("Ft. Detrick" formulation)
  - Recommended for those at high risk of exposure
- **Reviewed by ACIP 2007-2009; MMWR published 2010**

AVA plus CPG 7909 (Nuthrax®)

- **AVA plus CPG 7909 (a synthetic immunostimulatory oligonucleotide) investigated for its potential to achieve an accelerated immune response for anthrax PEP**
  - Synthetic oligonucleotides (ODN) with "CpG motifs"
    - trigger cells with toll-like receptors -- a type of pathogen recognition receptor expressed primarily on immune cells.
    - improve antigen presentation and vaccine-specific cellular and humoral responses.
  - Compared with AVA, AVA plus CPG 7909 is expected to achieve an accelerated immune response,
    - necessitating fewer injections
    - reduced amount of antigen to confer protection

BACKGROUND ON ANTHRAX ANTITOXIN

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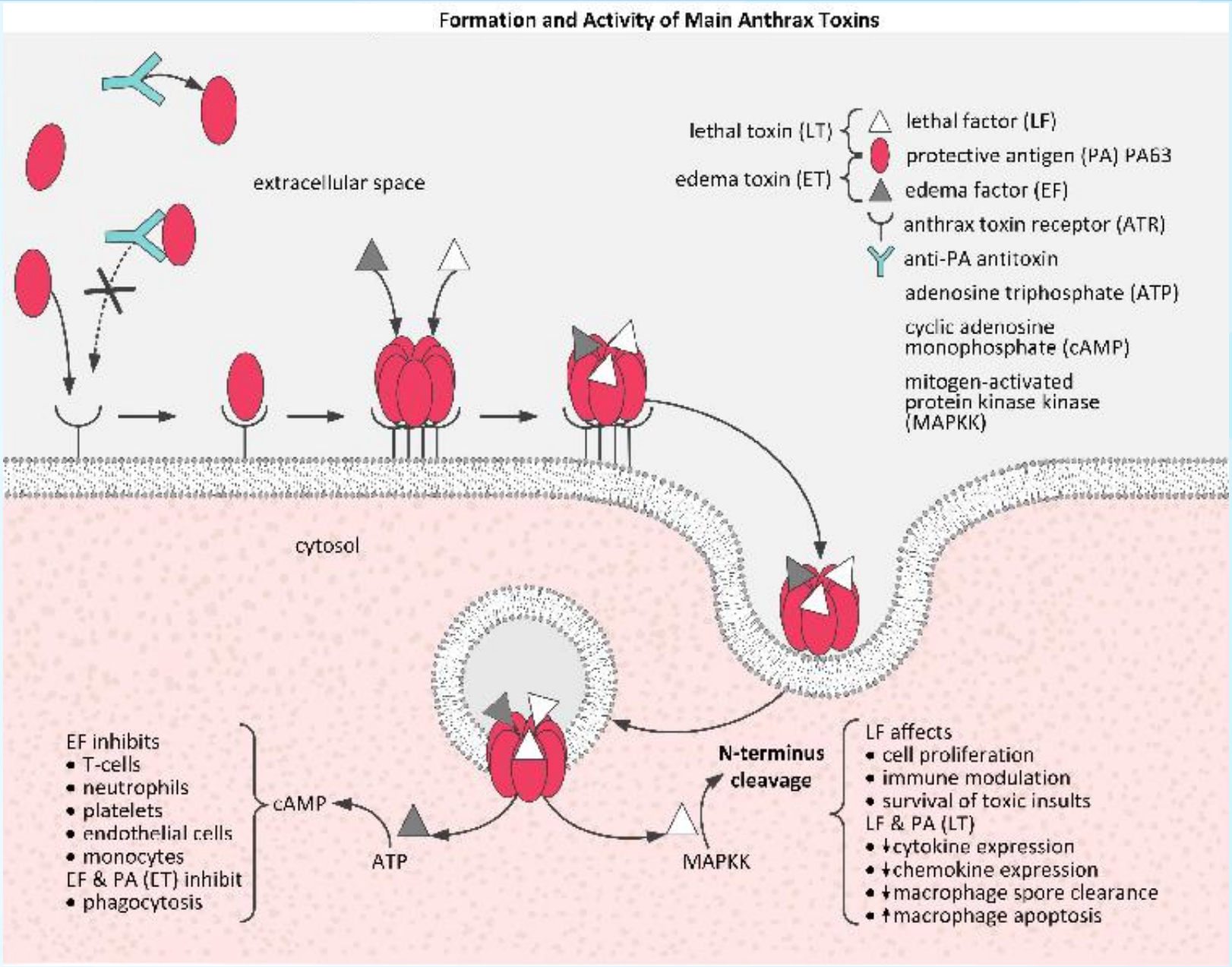
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cAMP
ATP
N-terminus cleavage
MAPKK
LF affects
• cell proliferation
• immune modulation
• survival of toxic insults
LF & PA (LT)
• ↓cytokine expression
• ↓chemokine expression
• ↓macrophage spore clearance
• ↑macrophage apoptosis

BACKGROUND ACIP ANTHRAX VACCINE RECOMMENDATIONS FOR ADULTS (MMWR 2010)

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Anthrax Vaccine Adsorbed (AVA) Uses

- **Pre-exposure Prophylaxis (PrEP) – for persons who have a risk of exposure to *Bacillus anthracis* through their occupation**
- **Post-exposure Prophylaxis (PEP) – for persons potentially exposed to *Bacillus anthracis***

AVA for PrEP

- **AVA is for the prevention of disease caused by *Bacillus anthracis*, in persons 18 through 65 years of age at high risk of exposure**
- **For PrEP, the vaccine is administered at a dose of 0.5ml and is administered as a**
  - Primary series: IM at 0, 1, and 6 months
  - Booster doses: IM at 12 and 18 months after initiation of the primary series, and at 1-year intervals thereafter for those at continued risk of infection

AVA for PrEP (continued)

It is recommended for:

- **Persons handling potentially infected animals in research settings or in areas with a high incidence of enzootic anthrax or when standards and restrictions are insufficient to prevent exposure to *B. anthracis***

- **Persons who perform certain types of laboratory work involving *B. anthracis***

AVA for PrEP (continued)

It is recommended for:

- **Persons involved in anthrax environmental investigations or remediation efforts**
- **Certain military personnel**
- **May be offered to persons involved in emergency response activities**

AVA for PEP

- ACIP recommends PEP for unvaccinated persons after exposure to aerosolized *B. anthracis* spores
- For PEP, AVA is administered as a 3-dose SC regimen at 0, 2, and 4 weeks in combination with 60 days of oral antimicrobials
- AVA series results in rapid anti-PA antibody production and augments the antimicrobial portion of PEP

AVA for PEP (continued)

- **With this combined antimicrobial-vaccine approach, the immune system benefits from**
  - Antimicrobial protection provided against germinating spores and vegetative cells of *B. anthracis*
  - While gaining enough time to establish immunological priming and establish anamnestic capability (*i.e.*, immunological memory).

Anthrax Antitoxin as PEP

- **Three antitoxins are approved for treatment of inhalation anthrax in combination with antimicrobials**
  - Raxibacumab
  - Anthim
  - AIGIV
- **Two antitoxins are also FDA-approved for prophylaxis when alternatives are not available or inappropriate**
  - Raxibacumab
  - Anthim

ACIP ANTHRAX VACCINE WORKGROUP

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ACIP Anthrax Work Group

- **Review operational issues related to mass vaccination following a wide-area release of *B. anthracis* spores**
- **New data since 2010 MMWR on**
  - Increased intervals between booster doses for PrEP
  - An alternative administration route for PEP
  - Modeling for an adequate immune response in humans based on nonhuman primate studies
- **Development of new formulation of AVA for licensure**
  - **AVA plus CPG 7909 adjuvant**
- **Review and advise on anthrax antitoxin for use as PEP**
- **ACIP Anthrax Vaccine Work Group reconvened spring 2017.**

Terms of Reference

- Review AVA data on reduced booster schedule for pre-exposure prophylaxis
- Review immunogenicity, safety, and logistical considerations for providing AVA via intramuscular versus subcutaneous route and provide evidence-based recommendations for administration as post-exposure prophylaxis
- Review AVA with CPG 7909 Adjuvant data and provide evidence-based recommendations for post-exposure prophylaxis.

Terms of Reference (continued)

- Review efficacy and immunogenicity data on reduced schedule and half-dose AVA use for post-exposure prophylaxis to prepare for potential emergency meeting for a mass casualty incident when AVA is a limited resource.
- Review and advise on use of AVA and antitoxin for post-exposure prophylaxis when no effective antimicrobials are available or have an absolute contraindication.

ACIP Anthrax Vaccine Work Group Members

- David Stephens - Chair
- Robert Atmar – ACIP Member
- Kathleen Neuzil – IDSA
- Richard Beigi – ACOG
- James Campbell – AAP
- Matthew Zahn – NACCHO
- Eric Deussing – DOD
- Judy Hewitt - NIH
- Kim Taylor – NIH
- Alexandra Worobec – FDA
- Julie Clifford - FDA
- Eric Espeland – BARDA
- Chia-Wei Tsai – BARDA
- Wendy Keitel – AVA SME
- Art Friedlander – Anthrax SME
- Phillip Pitman – Anthrax SME
- Andy Pavia – Peds SME
- William Bower – Anthrax SME
- Kate Hendricks – Anthrax SME
- Jarad Schiffer – Anthrax SME
- Charles Rose – Statistics SME
- Marie de Perio – NIOSH
- Mike McNeil – Vaccine Safety
- Jennifer Wright – Anthrax SME
- Jennifer Liang – Vaccine SME
- Yon Yu – Regulatory Affairs