CIPROFLOXACIN FOR PROPHYLAXIS OF CLINICAL DISEASE DUE TO INHALED *B. anthracis*

Anti-Infectives Advisory Committee Meeting

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Overview

- Inhalational anthrax
- Drugs for anthrax
- Microbiology of *Bacillus anthracis*
- Cipro pharmacology-animal and human
- Studies of post exposure prophylaxis

Inhalational anthrax

- First described British textile mills 19th c
- Woolsorters' or ragpickers' disease
- Largely an industrial / occupational infection
- Rare; US ~20 cases since 1900
- Hemorrhagic mediastinitis, with involvement of RES, CNS, and development of sepsis syndrome

Inhalational anthrax

- Clinical entity resulting from intentional use of aerosolized spores *B. anthracis*
- Mortality 80-100% clinically recognizable disease, even with appropriate therapy
- Penicillins and/or tetracyclines historically drugs of choice
- Reports of engineered *B. anthracis* strains PCN-R, TCN-R

Drugs for anthrax: regulatory status

- No drug is approved for **prophylaxis** of **inhalational** anthrax
- PCNs, TCNs with indications for **treatment** of clinical disease due to *B. anthracis*
- Programs for large scale use in civilian or military personnel, in contrast with practice of medicine, require an approved NDA indication or IND

Cipro

- First formulation (oral) approved US 1987
- Approved indications (17) include
  - lower respiratory tract infections
  - complicated intraabdominal infections
  - bone and joint infections
  - typhoid fever
- Used by >100 million patients in US

Cipro oral

- Approved doses 100-750 mg q 12 hour
- Proposed regimen anthrax prophylaxis:
  - Adult 500 mg q 12 hour
  - Pediatric 10-15 mg/kg q 12 hour
  - Duration 60 days

B. anthracis: Microbiology

- Spore forming
- Germinates into vegetative state under certain environmental conditions
- Vegetative state
  - encapsulated, toxin-producing: PA, EF, LF
  - generally PCN, TCN susceptible, 3% PCN-R
  - bioengineered strains with PCN-R, TCN-R

B. anthracis: Microbiology

Antimicrobial Susceptibility of 70 strains of *Bacillus anthracis*

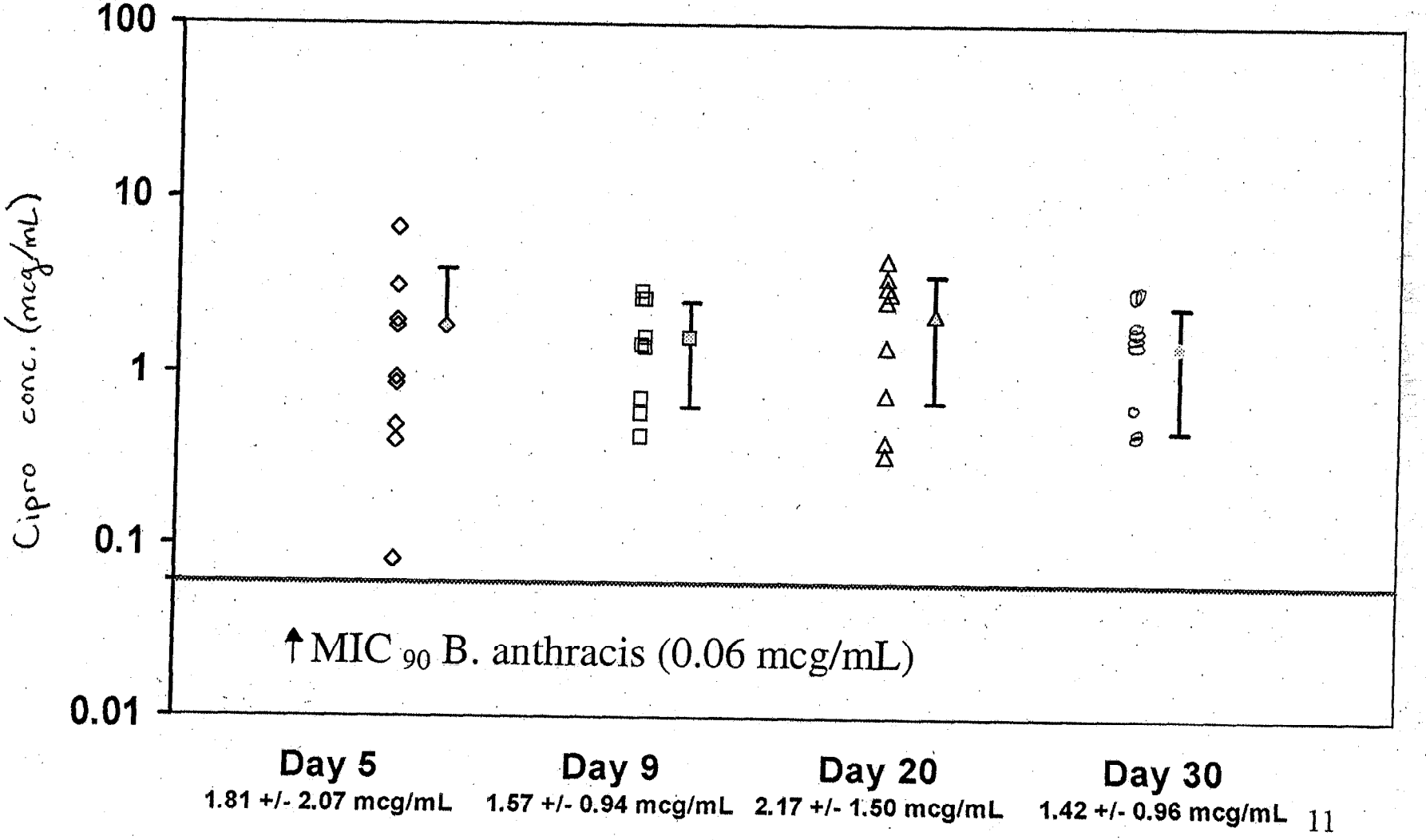
Drug	MIC Range (μg/mL)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)
Penicillin	0.015 - 64	0.06	0.125
Amoxicillin	0.03 - 64	0.06	0.125
Tetracycline	0.06 - 1.0	0.125	0.125
Ciprofloxacin	**0.03 - 0.06**	**0.06**	**0.06**

Cipro pharmacology: overview

- Peak and trough serum concentrations
  - Macaque monkey
  - Human
  - Comparison macaque and human

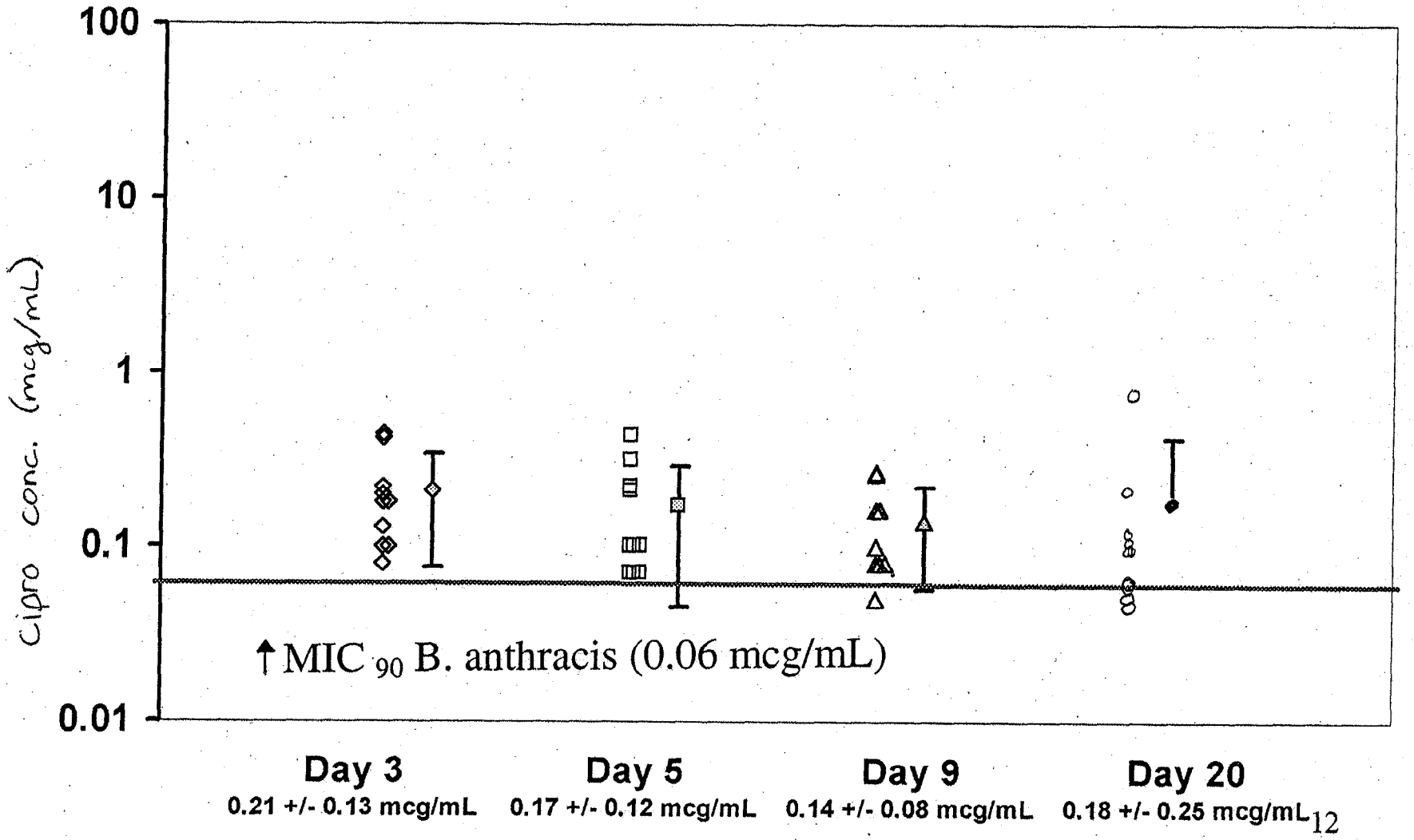
Ciprofloxacin Peak Concentrations - Monkeys

(Kelly et al 1992)



Ciprofloxacin Trough Concentrations - Monkeys

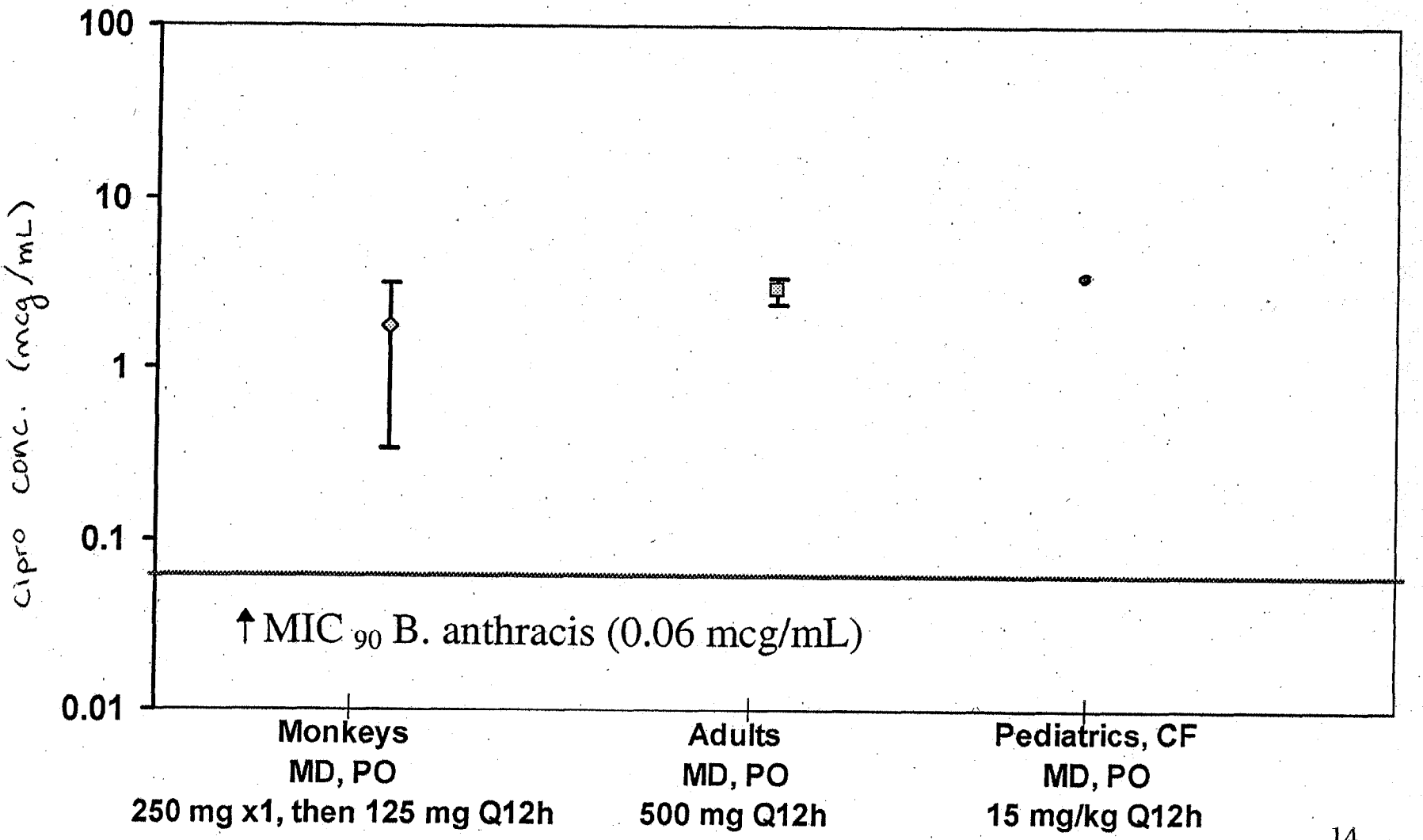
(Kelly et al 1992)



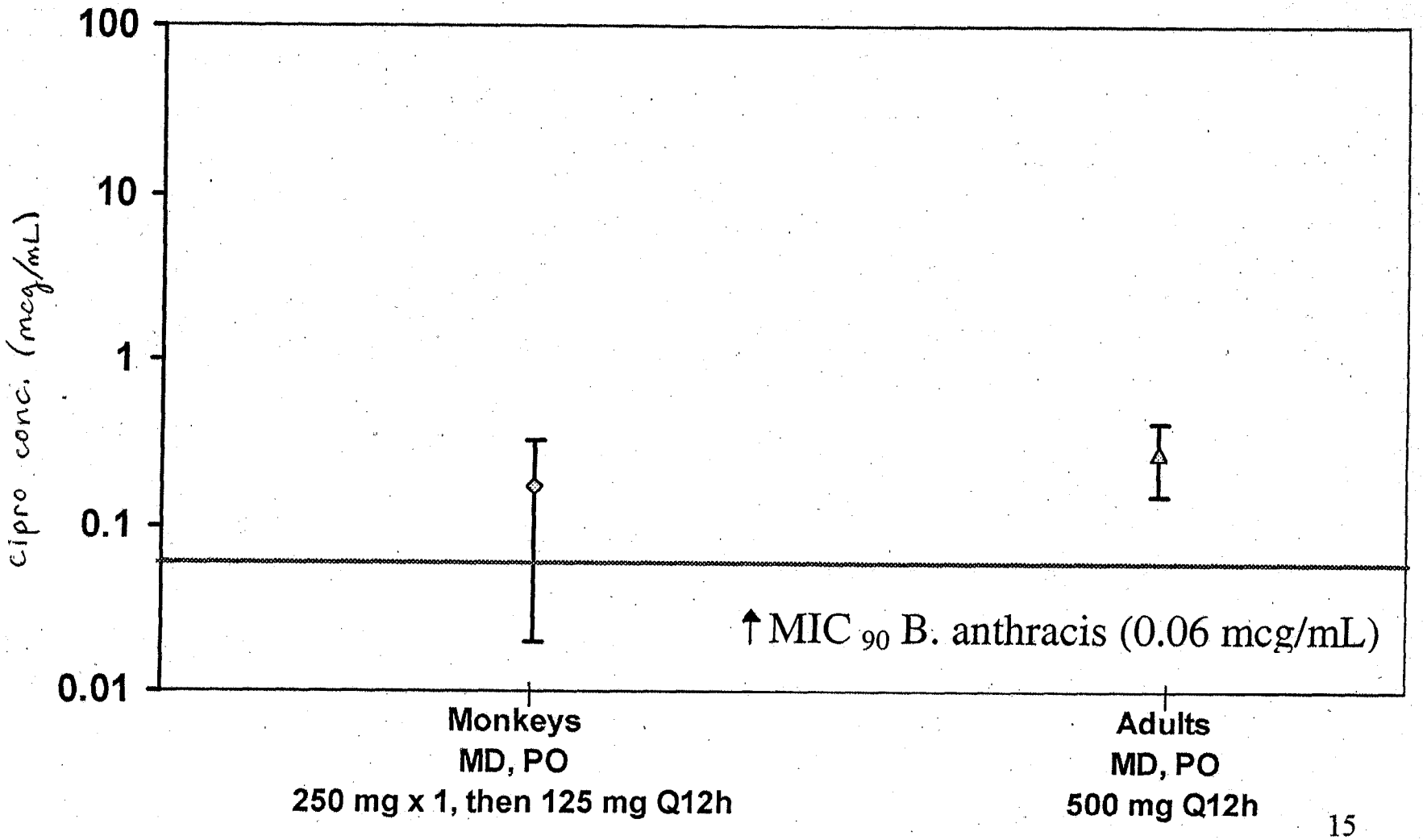
Ciprofloxacin Oral Steady State Pharmacokinetics

Population	Dose/ Regimen	$C_{max,ss}$ (µg/mL)	$C_{min,ss}$ (µg/mL)
Monkey	250 mg x 1, then 125 mg po Q12h (32 mg/kg x 1, then 16 mg/kg)	1.74	0.17
Human adult	500 mg Q12h (7.1 mg/kg)	2.97	0.2
Human pediatric cystic fibrosis	15 mg/kg Q12h	3.5	--

Ciprofloxacin Peak Concentrations - All



Ciprofloxacin Trough Concentrations - All



Comparison of drug levels with MIC_{90} *B. anthracis*

- Fluoroquinolones: killing is concentration dependent rather than time dependent
- Cmax/MIC $\geq$ 10 desirable range
- Cipro: *B. anthracis*
  - Cipro peak macaque ~33x MIC_{90}
  - Cipro peak human ~50x MIC_{90}

Inhalational anthrax: early theories of pathogenesis

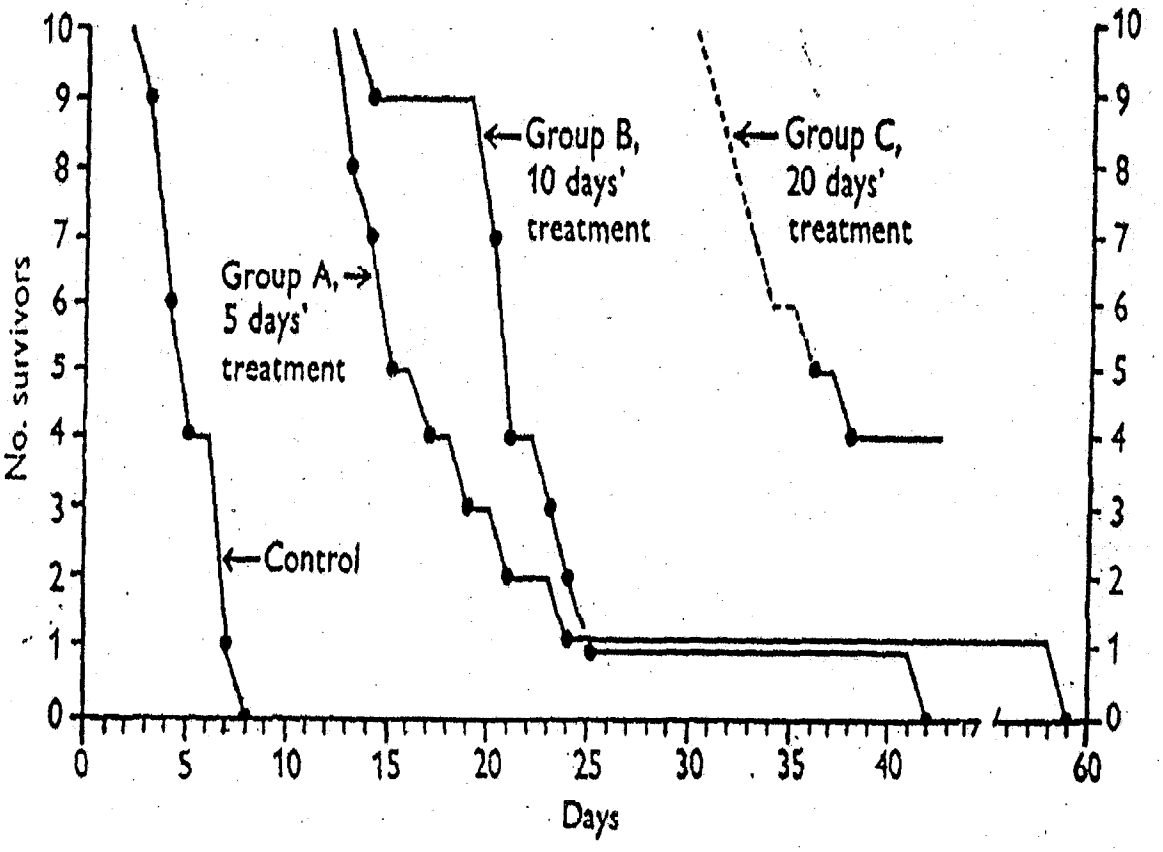
- Theory #1: Persistent spores
  - germination pulmonary macrophage (MØ)
  - toxin production/ early pathology mediastinal lymph nodes
- Theory #2: Acute bacterial infection
  - erosion bronchial mucosa
  - rapid germination pulmonary parenchyma
  - early pathology pneumonia

Early studies inhalational anthrax: post-exposure drug administration

- Post exposure PCN (Henderson et al 1956)
  - PCN 24 h post exp macaques for 5, 10, 20 days with controls
  - survival curves same slope as controls
  - only delay death

Survival curves

(Henderson et al 1956)



Spore clearance

(Henderson et al 1956)

Days after exposure	Estimated % original retention
42	15-20
50	2
75	0.5-1
100	trace

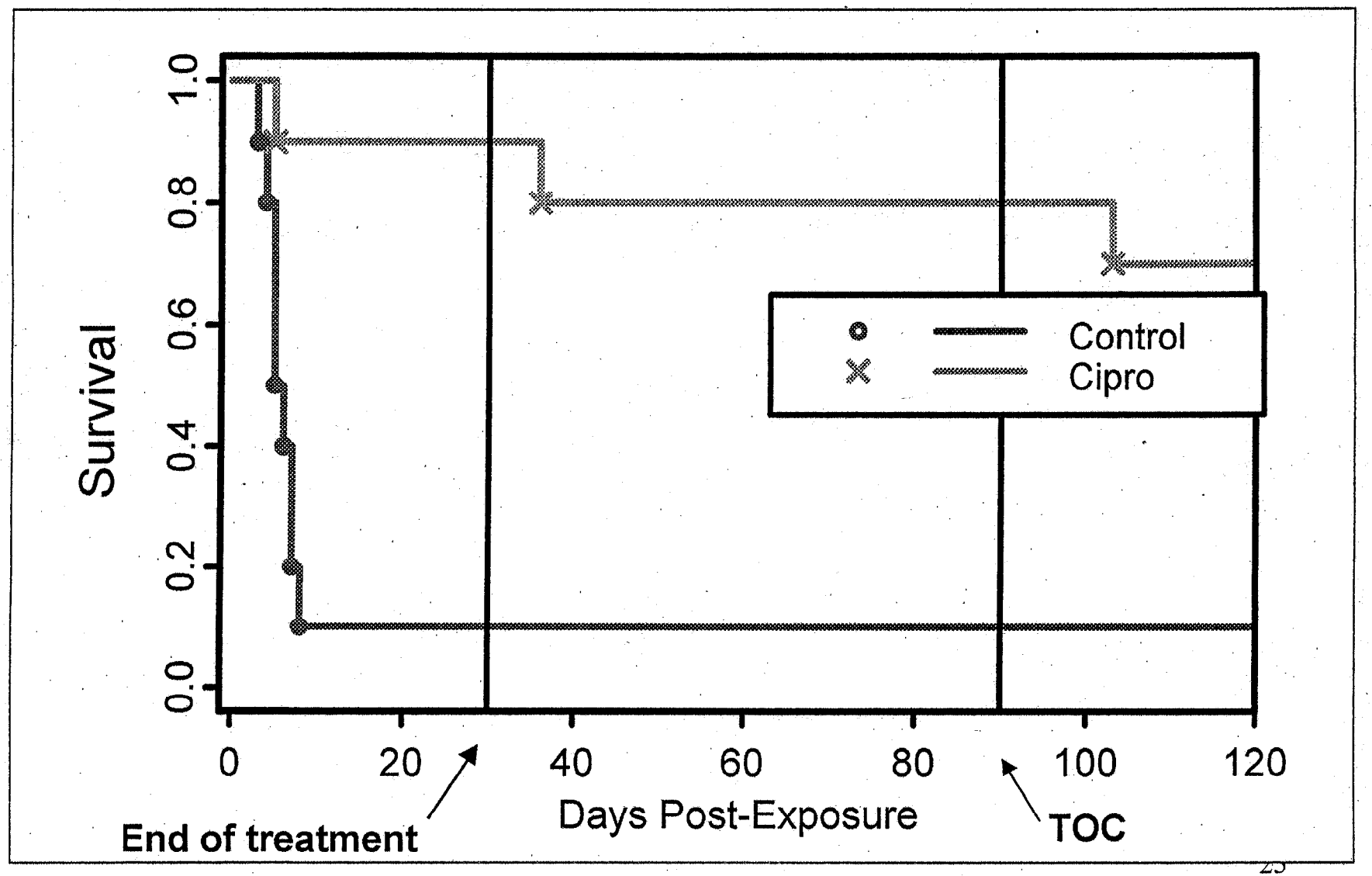
Early studies inhalational anthrax: spore clearance from lung (Ross 1957)

- Guinea pig: # spores reaching regional LN <<< # deposited pulmonary epithelium
- Differential staining: distinction of stages of spore development and vegetative state
- Different modes of spore exit from lung
  - **transported to regional LN via pulmonary MØ**
  - **phagocytosed spores passed into bronchioles**
  - **?spores lysed and destroyed in phagocytic cell**

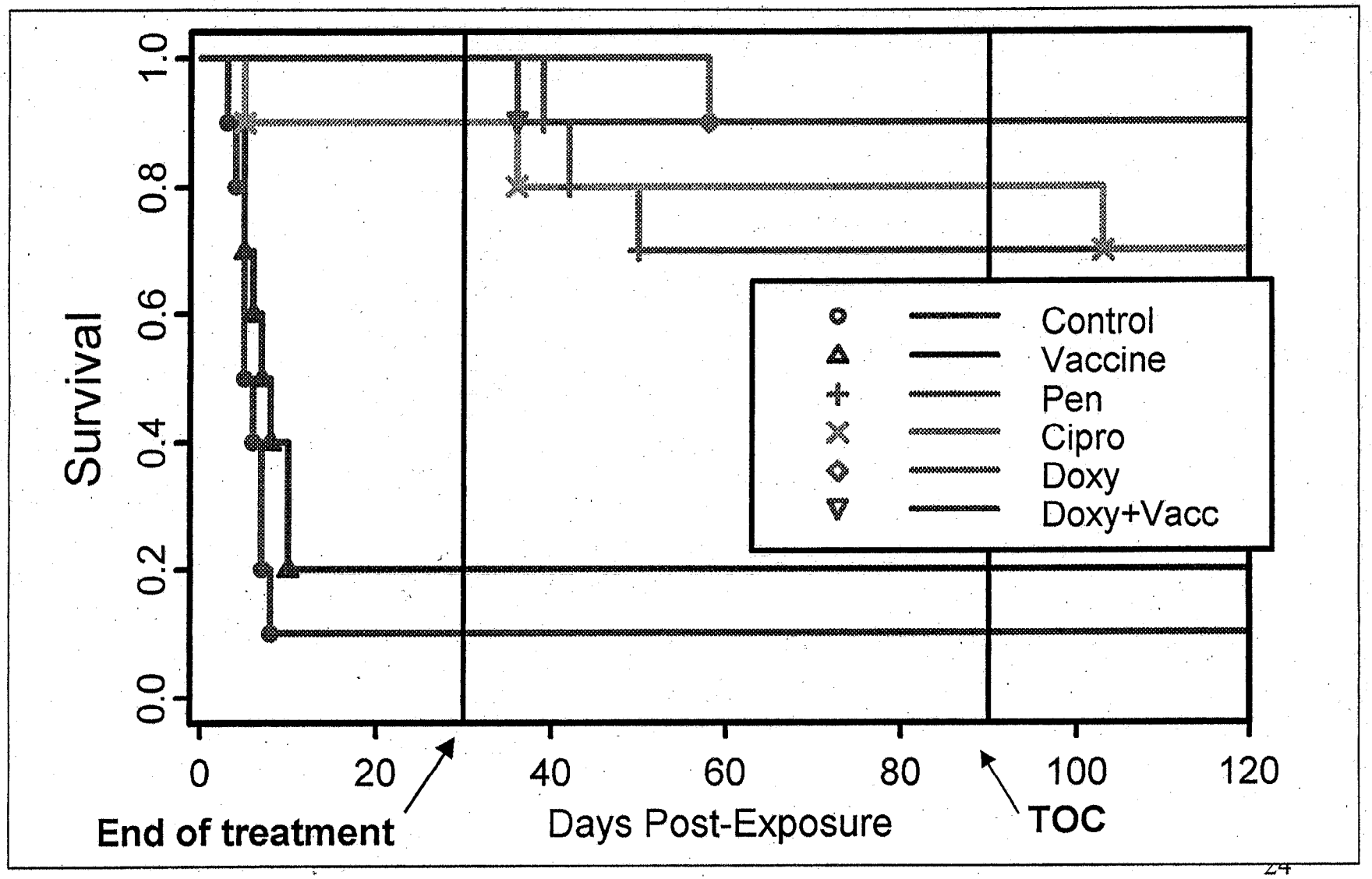
Inhalational anthrax: post-exposure drug administration (Friedlander et al 1993)

- 6 groups/10 animals each
  - 30 days antimicrobial: 1) ciprofloxacin, 2) doxycycline, 3) penicillin, 4) doxy + vaccine
  - 5) vaccine, 6) control
- Survival following aerosol challenge days 0-120
- Mortality rates
  - at 90 days (evaluable population)
  - up to 130 days (ITT population)

Challenge (from Friedlander et al 1993)



Challenge (from Friedlander et al 1993)



Intent-to-treat Analysis:

Including all cause of death up to re-challenge

Treatment	All deaths	P vs. control	95% CI of treatment - control
Control untreated	**9/10**		
Vaccine alone	**8/10**	**> 0.1**	**(-54, 37)**
Penicillin	**3/10**	**0.0198**	**(-89, -12)**
Ciprofloxacin	**3/10**	**0.0198**	**(-89, -12)**
Doxycycline	**1/10**	**0.0011**	**(-98, -36)**
Doxy + vaccine	**1/10**	**0.0011**	**(-98, -36)**

P-value was calculated using a two-tailed Fisher's exact test.
95% confidence interval was calculated using an exact method.

Evaluable Population Analysis:

Cause of death proven to be due to Anthax (TOC=90)

Treatment	Anthrax deaths	P vs. control	95% CI of treatment - control
Control untreated	**9/10**		
Vaccine alone	**8/10**	**> 0.1**	**(-54, 37)**
Penicillin	**3/10**	**0.0198**	**(-89, -12)**
Ciprofloxacin	**1/9**	**0.0011**	**(-98, -35)**
Doxycycline	**1/10**	**0.0011**	**(-98, -36)**
Doxy + vaccine	**0/9**	**0.0001**	**(-100, -52)**

P-value was calculated using a two-tailed Fisher's exact test.
95% confidence interval was calculated using an exact method.

Prevention of inhalational anthrax: duration of drug administration

- 5, 10, 20 days too short
- 30 days look better
- Of the ciprofloxacin cohort, one anthrax death at 36 days
- Spore load decreases over time
- Is there a minimum?

Prevention of inhalational anthrax: human epidemiology

- Sverdlovsk 1979 published account: longest incubation fatal case 43 days
  - Patient #42
- Industrial exposure
  - nonimmunized mill workers inhale 150-700 anthrax-contaminated particles $\leq 5\mu$/ shift
  - clinical disease rare
  - likelihood of development of anthrax independent of duration of employment

Summary: Inhalational anthrax

- Rare, rapidly progressive disease with very high mortality
- Little opportunity to improve outcome with treatment once clinical disease recognized
- Identified as a clinical manifestation of a biological agent of highest potential concern

Summary: Inhalational anthrax

- Currently no drug approved for prophylaxis
- Cannot be studied in humans
- Non-human primate model demonstrates similar pathology and mortality as humans

Summary: Ciprofloxacin

- Post-exposure administration in primate model shown to significantly improve survival compared with placebo
- Comparable blood levels achieved with
  - dose used* for successful prophylaxis in primate model of inhalational anthrax
  - 500 mg po q 12 hours in adults
  - 15 mg/kg po q 12 hours in children
- Blood levels achieved experimental animals and humans ~30-50x MIC_{90} *B. anthracis*
  - *250 mg followed by 125 mg q 12 hr

Summary: Ciprofloxacin

- Broad array of indications with substantial clinical experience
- Well-characterized safety database

Summary:
Prophylaxis of inhalational anthrax

- Prophylaxis an effort to reduce risk
- Ciprofloxacin survival better than placebo following 30-day regimen
- Epidemiologic data suggest duration of drug administration at least 45 days
- Duration of proposed regimen is 60 days

Question #1 for committee

- Do the data presented support the safety and efficacy of ciprofloxacin for post-exposure prophylaxis of inhalational anthrax?

Question #2 for committee

- If yes, is 60 days an appropriate duration of ciprofloxacin administration for this indication?

Acknowledgements

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