Tuberculosis and Elephants: The “real” elephant in the room

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WEBINAR INTRODUCTION
Webinar Introduction

- **Moderator** - Kevin Fennelly, MD, MPH
- **Presenter** - Ramiro Isaza, DVM, MPH

Understand the basics of elephant TB as an “elephant” disease

- Biology of the disease in elephants
- Prevalence in captive elephants
- Diagnostic challenges of elephants
- Treatment of TB in elephants
Webinar Introduction

- Introduce the concept that *M. tuberculosis* in elephants is a “zoonotic” agent
  - “One health” in real life

Webinar Introduction

- Consider the implications of elephant tuberculosis as a novel public health hazard and occupational disease
Webinar Introduction

Scenario #1
- Elephants are “coming to town” and the local media wants to know what the tuberculosis public health risks are to the general public
  ▶ What would you say to the media?

Webinar Introduction

Scenario #2
- Patient is asking for annual PPD because she works with elephants at a local zoo
  ▶ What would you tell this patient about her risks and need for a PPD?
QUESTION SET #1

CASE REPORT
Signalment and Husbandry

- Asian elephant
- Male
- 14 y. o. (“adolescent”)
- Captive born
- Typical hay based diet

History and Physical Examination

- History of consistent weight gain and growth
**History and Physical Examination**

- History of consistent weight gain and growth
- Normal examination

**Unexpected Laboratory Result**

- *M. tuberculosis* cultured from a routine trunk-wash sample
BACKGROUND ON ELEPHANT TUBERCULOSIS

ASIAN ELEPHANT NATURAL HISTORY
Elephant Basics

Asian Elephant  
(*Elephas maximus*)

African Elephant  
(*Loxodonta africana*)  
(*Loxodonta cyclotis*)
Elephant Basics

- Asian elephant populations
  - Endangered Species (CITES Appendix 1)

Elephant Basics

- Asian elephant populations
  - Habitat Destruction
**Elephant Basics**

- Asian elephant populations
  - About 30 thousand elephants in the wild

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**Elephant Basics**

- Captive Asian elephant populations in Asian range countries
  - About 10 thousand in captivity
Elephant Basics

- North American Captive Asian elephant populations
  - About 280

Elephant Basics

- About 100 in FL
Elephant Basics

Elephant’s “value”
- Endangered species
- Charismatic megavertebrate
- Monetary investment

TUBERCULOSIS IN ELEPHANTS
M. tuberculosis in Asian elephants

- *M. tuberculosis* in Asian elephants
  - Not *M. bovis*
  - Not an atypical mycobacteria
  - A primary human pathogen in an animal
History of Elephant TB in U.S.

- Several “old” case reports
- 1996 Elephant TB “emerges”
History of Elephant TB in U.S.

- Several “old” case reports
- 1996 Elephant TB “emerges”
- Advisory panel formed


Tuberculosis in Elephants (US)

Prevalence of M. tuberculosis (2001)
- About 2-4% of the population

Prevalence of M. tuberculosis (2011)
- About 18% of the population
Prevalence of *M. tuberculosis*

- Elephant cases of “Tb complex”
  - About 50 total cases (1994-2010)
    - Asian elephants (46 *M. tb*)
    - African elephants (3 *M. tb*)
      - 1 *M. bovis*
Tuberculosis in Elephants (US)

Prevalence of *M. tuberculosis*

- Is the prevalence really increasing?
  - Increased testing since 1997

Tuberculosis in Elephants (US)

Prevalence of *M. tuberculosis*

- Is the prevalence really increasing?
  - Increased testing since 1997
  - Calculation of prevalence
Prevalence of M. tuberculosis

- Is the prevalence really increasing?
  - Increased testing since 1997
  - Calculation of prevalence
    - Prevalence is not (total cases / current pop.)
    - 46 / 246 = 18.7%

(Tuberculosis in Elephants (US)

(Mikota and Maslow, 2011, Tuberculosis, 91:208-211.)
Prevalence of *M. tuberculosis*

- Yearly point prevalence over the past 50 years using SSP studbook information

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**Prevalence of Elephant Tuberculosis**

![Graph showing the prevalence of elephant tuberculosis over the past 50 years](image)
Prevalence of *M. tuberculosis*

- Median since 1997 = 5.0%
- Range = 1.2 – 5.8%
Tuberculosis in Elephants (US)

**Incidence Density of M. tuberculosis**
- Annual incidence density over the past 50 years using SSP studbook information
  - 8 cases /1000 elephant years since 1997
History of Elephant TB Worldwide

- Swedish zoo
- Nepal
- India
- Thailand
- Sri Lanka

- Wild elephants?
Pathology of Elephant TB

Post-Mortem Diagnosis
- Necropsy

Pathology of elephant tuberculosis

Southeastern National Tuberculosis Center
Pathology of Elephant TB

- Pathology of elephant tuberculosis

Pathology of Elephant TB

Post-Mortem Diagnosis
- Histopathology
- Acid-Fast staining
- Immunohistochemistry
Pathology of Elephant TB

Post-Mortem Diagnosis

- Culture
- Molecular diagnostics

Pathology of Elephant TB

- “Textbook” clinical signs
  - Weight loss
  - Coughing
  - Exercise intolerance
  - Rare presentation!
Pathology of Elephant TB

● “Typical” clinical signs
  ▶ Normal physical examination

Pathology of Elephant TB

● Incidental necropsy finding signs
Elephant TB Diagnostics

Ante-Mortem Diagnosis
- Elephants apparently have latent TB

Elephant TB Diagnostics

Ante-Mortem Diagnosis
- Symptoms?
- TB skin tests?
- Radiographs or CT?
- Bronchoscopy?
Elephant TB Diagnostics

Ante-Mortem Diagnosis
- Culture (Trunk Wash)
Elephant TB Diagnostics

- M. tuberculosis was cultured for the second time from a trunk wash sample

Elephant TB Diagnostics

Ante-Mortem Diagnosis
- Culture (Trunk Wash)
  - Definitive diagnosis
  - Drug sensitivity
  - DNA for genotyping
Elephant TB Diagnostics

Ante-Mortem Diagnosis
- Molecular diagnostics?
- Other tests?

Elephant TB Diagnostics

Ante-Mortem Diagnosis
- TB Serology?
Elephant TB Diagnostics

Ante-Mortem Diagnosis
- Serology as an epidemiological tool

Elephant TB Diagnostics

Ante-Mortem Diagnosis
- ElephantTB STAT-PAK®
Elephant TB Diagnostics

Ante-Mortem Diagnosis
- ElephantTB STAT-PAK®
- and MAPIA™

Interferon assays (IGRAs)?
Elephant TB Diagnostics

Ante-Mortem Diagnosis

- Which test is the best?

Treatment of Tuberculosis

Multi-Drug Therapy

- Pharmacokinetics
Treatment of Tuberculosis

Multi-Drug Therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (mg/kg)</th>
<th>Route</th>
<th>Formulation</th>
<th>Target conc (µg/ml)</th>
<th>Cmax (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>5</td>
<td>Oral or rectal</td>
<td>premixed suspension</td>
<td>3-5</td>
<td>1-2</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Oral</td>
<td>powder</td>
<td>3-5</td>
<td>0.5-1</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>10</td>
<td>Oral only</td>
<td>powder</td>
<td>8-24</td>
<td>2-4</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>30</td>
<td>Oral or rectal</td>
<td>powder</td>
<td>20-60</td>
<td>1-2</td>
</tr>
<tr>
<td>Ethambutel</td>
<td>30</td>
<td>Oral only</td>
<td>powder</td>
<td>2-5</td>
<td>1-2</td>
</tr>
</tbody>
</table>


Treatment of Tuberculosis

Multi-Drug Therapy

- Cost = $100,000 / Year
TUBERCULOSIS AS A ZOONOTIC DISEASE

Zoonotic Potential of Tuberculosis

Zoonotic Disease
- “Classic” zoonosis
- “Reverse” zoonosis
- “Shared” zoonosis
Zoonotic Potential of Tuberculosis

M. tuberculosis in Other Species

- Primates
- Dogs, Cats, Ferrets
- Parrots
- Guinea pigs

Zoonotic Potential of Tuberculosis

- One case report of zoonotic infection
Zoonotic Potential of Tuberculosis

Epidemiological Studies

- LA Zoo (Oh, 2002)
- Hawthorne private collection (Michalak, 1998)
- Tennessee private collection (Murphree, 2011)

Elephant workers

- Close elephant contact
- Work in closed barns
Zoonotic Potential of Tuberculosis

Traveling elephant workers
- Constant travel
- Share close living quarters
- Foreign born
- Other TB risk factors

Zoonotic Potential of Tuberculosis

Veterinarians working with elephants
- Trunk washing procedure
- Treatment
- Necropsy
Zoonotic Potential of Tuberculosis

Environmental factors

- Mycobacterium tuberculosis Risk for Elephant Handlers and Veterinarians (Davis, 2001)
Employee Health and Safety

- Monitoring programs for employees

**Zoonotic Potential of Tuberculosis**

**EMLOYEE HEALTH AND SAFETY**

**All facilities:**

- New employees should be tested prior to contact with elephants.
- All employees in direct contact with elephants should be tested for TB.
- Any employee with a positive test should be evaluated for active TB.
- Employees with active TB should be removed from the elephants.

EMPLOYEE HEALTH AND SAFETY

Facility housing culture-positive elephants should develop a program to protect employees from TB exposure:

- Use of respiratory (N95) HEPA filtered masks during all direct or indirect contact with infected animals, such as cage cleaning, medication administration, feeding, watering, etc.
- Use of separate implements for infected animals.
- Contact the local public health department further guidelines.


WHAT WE THINK WE “KNOW” ABOUT ELEPHANT TUBERCULOSIS
Review of Elephant TB

- M. tuberculosis in Asian elephants
- Prevalence of about 6%
- Usually a pulmonary infection
- Latency occurs in elephants

WHAT WE REALLY DON’T KNOW ABOUT ELEPHANT TUBERCULOSIS
Elephant Epidemiology

- Where are elephants first becoming infected with *M. tuberculosis*?
  - Elephant to elephant in Asia
  - Mahout to elephant in Asia
  - Keeper to elephant in North America
  - Elephant to elephant in North America

Elephant Epidemiology

- How is tuberculosis maintained within elephant populations?
  - Elephant to elephant
  - Extensive latent infections
  - Reverse zoonosis
Elephant Epidemiology

- What is the occupational risk of working around infected elephants?
  - A case report and a few preliminary epidemiological studies
  - How many people are actually getting infected?

**QUESTION SET #2**
Case Discussion 1

- Elephants are coming to the local zoo
  - The local media wants to know what the tuberculosis risks are to the general public visiting the zoo
Case Discussion 1

- Three new elephants will be transported to the local zoo for breeding
  - One has a positive antibody test
  - All cultured negative for four years
  - None have history of exposure

Case Discussion 1

- As a public health expert, the local media is asking you for information about elephant tuberculosis
QUESTION SET #3

Case Discussion 2

- Patient is asking for annual PPD because she works with five elephants at a local zoo
Case Discussion 2

- 35 years old
- Hispanic, Female
- Medical history:
  - Previous monkey bite 5 years ago
  - Mild, controlled asthma
  - HIV negative

Case Discussion 2

- Work History
  - Worked with primates 6 years
  - Worked with elephants 4 years
- PPD HX – unknown
- No current symptoms of TB
Case Discussion 2

- The patient works with a culture positive elephant at her zoo

QUESTION SET #4
Case Discussion 3

Linked Outbreaks in the Literature

- California index cases
- Hawthorne private collection
- Tennessee private rescue collection

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Case Discussion 3

Tennessee private rescue collection

- 46/57 employees interviewed
  - 30 elephant workers (caregivers)
  - 11 administrators
  - 5 maintenance workers
Case Discussion 3

Tennessee private rescue collection

- 9 were PPD positive, no clinical signs
  - 8 had conversions during 2009
  - One elephant was culture positive and not treated between 2008 and 2010

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Table 1

<table>
<thead>
<tr>
<th>Potential risk factor</th>
<th>TST conversion/risk factor, no. (%)</th>
<th>TST conversion/no risk factor, no. (%)</th>
<th>Relative risk (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreign born</td>
<td>2/6 (33)</td>
<td>7/40 (18)</td>
<td>1.01 (0.51-7.10)</td>
</tr>
<tr>
<td>International travel past 5 y</td>
<td>5/10 (26)</td>
<td>4/27 (15)</td>
<td>1.78 (0.56-5.76)</td>
</tr>
<tr>
<td>Exposure to person(s) with TB</td>
<td>0/4 (0)</td>
<td>9/42 (21)</td>
<td>NC</td>
</tr>
<tr>
<td>Previous health care facility work</td>
<td>1/1 (100)</td>
<td>8/88 (9)</td>
<td>0.59 (0.06-4.10)</td>
</tr>
<tr>
<td>Previous correctional facility work</td>
<td>0/4 (0)</td>
<td>9/42 (21)</td>
<td>NC</td>
</tr>
<tr>
<td>Previous homeless shelter work</td>
<td>0/1 (0)</td>
<td>9/45 (20)</td>
<td>NC</td>
</tr>
<tr>
<td>Close contact with elephant(s)</td>
<td>2/11 (18)</td>
<td>7/95 (16)</td>
<td>0.94 (0.33-2.73)</td>
</tr>
<tr>
<td>Quarantine area exposure during 2009</td>
<td>0/12 (0)</td>
<td>2/2 (100)</td>
<td>20.21 (2.41-149.09)</td>
</tr>
</tbody>
</table>

*TST, tuberculin skin test; CI, confidence interval; TB, tuberculosis; NC, not computed.

*Relative risk and confidence intervals were not computed when at least 1 cell contained zero.
Case Discussion 3

Tennessee private rescue collection
- Quarantine barn exposure was defined as being in the quarantine barn for more than 4 hours during 2009

- 13/46 workers exposed
- 8/13 converted during the exposure
- Elephant workers (8), administrative (3), maintenance workers (2)
Case Discussion 3

Tennessee private rescue collection

Table 2
Exact relative risk for potential risk factors for latent Mycobacterium tuberculosis infection among 12 employees who worked in the quarantine area of an elephant reserve, Tennessee, USA, 2009a

<table>
<thead>
<tr>
<th>Potential risk factor</th>
<th>TST conversion/risk factor, no. (%)</th>
<th>TST conversion/no risk factor, no. (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Close contact with elephant(s)</td>
<td>1/3 (33)</td>
<td>7/10 (70)</td>
<td>0.48 (0.09-2.40)</td>
</tr>
<tr>
<td>Participated in elephant trunk washes</td>
<td>0/1 (0)</td>
<td>8/12 (67)</td>
<td>NC</td>
</tr>
<tr>
<td>Pressure washed barn walls and floors</td>
<td>5/6 (62)</td>
<td>3/5 (60)</td>
<td>1.04 (0.42-2.53)</td>
</tr>
<tr>
<td>N95 respirator fit tested annually</td>
<td>2/5 (40)</td>
<td>6/8 (75)</td>
<td>0.53 (0.17-1.66)</td>
</tr>
<tr>
<td><em>Always</em> compliant with N95 wear</td>
<td>2/5 (40)</td>
<td>6/8 (75)</td>
<td>0.53 (0.17-1.66)</td>
</tr>
</tbody>
</table>

*TST, tuberculin skin test; CI, confidence interval; NC, not computed.

*Relative risk and confidence intervals were not computed when at least 1 cell contained zero.
Case Discussion 3

Tennessee private rescue collection
- Poor ventilation
- Unrestricted air flow
- Power washers
- Atypical mycobacteria
QUESTION SET #5

CONCLUSIONS
## Tuberculosis in Elephants

<table>
<thead>
<tr>
<th></th>
<th>Human</th>
<th>Elephant</th>
<th>Monkey</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Latent infection (Non-Infectious)</strong></td>
<td>Long term</td>
<td>Unknown Length</td>
<td>N/A - Most mammal species do not have recognized latent periods.</td>
</tr>
<tr>
<td></td>
<td>No clinical signs</td>
<td>No clinical signs?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PPD positive, Serology positive</td>
<td>Skin test?, Serology positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Effective prophylactic treatment</td>
<td>Untested prophylactic treatment</td>
<td></td>
</tr>
<tr>
<td><strong>Active disease (Infectious)</strong></td>
<td>Usually patients have symptoms of disease</td>
<td>Inconsistent clinical signs of disease</td>
<td>Obvious symptoms of disease</td>
</tr>
<tr>
<td></td>
<td>Confirmatory radiographs, CT, and bronchoscopy</td>
<td>No Confirmatory Imaging available due to size</td>
<td>Confirmatory radiographs, CT, and bronchoscopy</td>
</tr>
<tr>
<td></td>
<td>Culture positive with associated drug sensitivity</td>
<td>Culture positive with associated drug sensitivity</td>
<td>Culture positive with associated drug sensitivity</td>
</tr>
<tr>
<td></td>
<td>Reportable</td>
<td>Reportable</td>
<td>Reportable</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Curative Multi-Drug Treatments Well Established</td>
<td>Multi-drug treatment options proposed but untested</td>
<td>Euthanize - no treatment options</td>
</tr>
</tbody>
</table>

### QUESTION SET #6

- TB and Elephants
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Case Discussion 3

Selected References: