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Summary of Fourth Annual Tuberculosis and Elephants Workshop

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The Ringling Bros. Center for Elephant Conservation (CEC), and the International Elephant Foundation (IEF) hosted the fourth Annual Tuberculosis and Elephants Workshop on November 3-4, 2010 in Florida, USA. Workshop participants included recognized experts in infectious disease, specifically tuberculosis and pharmacology, veterinarians, and elephant managers. The workshop started with a review of information from the previous 'Tuberculosis and Elephants Workshop' hosted in 2009 by the St. Louis Zoo, Ringling CEC, and IEF. The first three Tb workshops identified priorities for increasing the understanding of tuberculosis (Tb) in elephants, and participants engaged in focus groups to develop specific projects to address those priorities.

Based on the outcomes of the 2009 Tb workshop, the goals of this year's workshop were identified:
- Elucidate current issues with Tb diagnosis in elephants
- Elucidate current issues with Tb treatment in elephants
- Develop proposals to address alternative Tb treatment issues in culture positive elephants
- Develop research proposals and identify potential partners to address alternative Tb treatment issue for prophylactic treatment of elephants

Two presentations were given on the topic of Tb treatment. In the first, Dr. Ellen Wiedner VMD, DACVIM (Ringling CEC, Florida, USA) reviewed a survey from 2007 looking at effects of Tb treatment on elephants in facilities within the USA (Wiedner & Schmitt 2007). The survey identified 17 elephants treated for Tb after having positive trunk wash cultures. Out of those animals, 14 experienced serious side effects that were significant enough to stop treatment. The Tb treatment side effects were varied and included lack of appetite, ocular issues, colic, anemia, weight loss, behavioral changes, and ventral edema. Some of the side effects even appear to be permanent (i.e. corneal scarring, ataxia, sterility).

Participant discussions addressed the fact that the current Tb treatment outlined in the U.S. Department of Agriculture (USDA) mandated "Guidelines for the Control of Tuberculosis in Elephants" is based on out-of-date human guidelines from 1994, and that monitoring blood work for drug-related side effects, as recommended by these guidelines, does not result in effective monitoring of possible side effects in elephants. There are currently no reliable or validated liver enzyme or liver function tests for elephants. Contrary to most mammals, elephants produce bile alcohols, not bile acids, and no tests exist for bile alcohols. Therefore, using typical serum biochemical tests in elephants to document liver toxicity from anti-tuberculosis drugs is not possible. Additionally, the American Thoracic Society provided updates in human Tb treatment recommendations in 2007 in response to recognition of severe liver toxicity and other side effects associated with anti-tuberculosis drugs in humans. These recommendations for human Tb treatments include: shorter duration, intermittent dosing, and new drug development.

Based on data collection and literature searched, there is an urgent need to review current Tb treatment protocols in elephants to ensure the health and welfare of Tb culture positive animals (Wiedner & Schmitt 2009).

Dr. Erica Wilson DVM (Dickerson Park Zoo, Missouri, USA) presented a case report on an older Asian female elephant. This female, in her early 60's, was healthy and normal, and over the years her trunk wash cultures had always been negative. In the course of routine Tb testing, the new Tb blood tests (Elephant Tb Stat-Pak and MAPIA) currently required by the USDA as part of testing for tuberculosis in elephants, indicated the elephant was reactive on the tests. Based on the serology results, the elephant was treated for Tb under the 2008 USDA Tb Guidelines. However this elephant had severe reactions to the Tb treatment drugs and subsequently died. On post-mortem no signs of Tb were found. This is the second such case in the United States, and clearly raises significant concerns about the validity of initiating Tb treatment based only on a serology test. It also demonstrates an urgent need for further research about Tb treatment options for elephants.

Much discussion ensued about the decision by USDA to mandate blood testing for tuberculosis, via the Elephant Tb Stat-Pak and MAPIA tests, for all elephants in the U.S. between March 2010 and March 2011. The results provided by this testing method require critical review, as the nature of the testing allows varied interpretation of the results. Demonstrating that a test can repeatedly identify a set of pre-selected samples demonstrates repeatability not validity. In addition, the MAPIA test is only a confirmatory test for the Elephant Tb Stat-Pak, and not for tuberculosis. As a confirmatory test to the Elephant Tb Stat-Pak, the MAPIA separates the antibodies detected into individual bands, rather than one band as used in the Elephant Tb Stat-Pak test. If reactive, then the Elephant Tb Stat-Pak is confirmed. If non-reactive, then the Elephant Tb Stat-Pak is considered a false positive. In a recent publication (Greenwald et. al. 2009) 54% (12/22) of Elephant Tb Stat-Pak positive elephants from a group of 63 animals were determined to be in this false positive category (i.e. Elephant Tb Stat-Pak positive, MAPIA negative, and Tb culture negative).

Furthermore, elephants that have chronic inflammatory issues may test positive on Elephant Tb Stat-Pak. This suggests that the serological tests may be identifying markers of inflammation, which again demonstrates that these tests are not specific enough for Tb diagnosis. Currently ChemBio (manufacturer of the Elephant Tb Stat-Pak and MAPIA tests) runs the (multiple antigen) antibody test, and, based on proprietary criteria, makes a determination confirming or not confirming the reactive Elephant Tb Stat-Pak results. These results should be verified independently. The ChemBio Dual Pathway Platform (DPP) test is currently not available for use in the United States, but is under review for licensure. If approved for use in the U.S., it will replace the MAPIA testing to confirm the Elephant Tb STAT-PAK test Interestingly, according to a recent publication (Landolfi et al. 2010) much of the Tb testing of elephants in Asian range countries has primarily relied on serology using the Elephant Tb Stat-Pak and MAPIA tests, and not on cultures of the Tb organism. Data about the overall percentage of elephants in Asia with confirmed culture positive diagnosis of Tb is still not available. In at least one Asian elephant range country with a known high burden of tuberculosis in the human population, no clinical or pathological signs considered suspicious for tuberculosis in elephants have been noted to date, and no diagnosis of Tb in elephants have been confirmed. (C. Stremme, pers. comm.)

The consensus, from experienced veterinarians and Tb researchers present at the Tb workshop, was that prior to relying on Tb serology testing in elephants, there needs to be further study of the elephant immune system and general immunology to better understand how elephants are affected by Tb.

The last topic addressed during the workshop was whether there is a potential occupational health risk for people who work with elephants to develop tuberculosis. The workshop participants' consensus was that there is a need
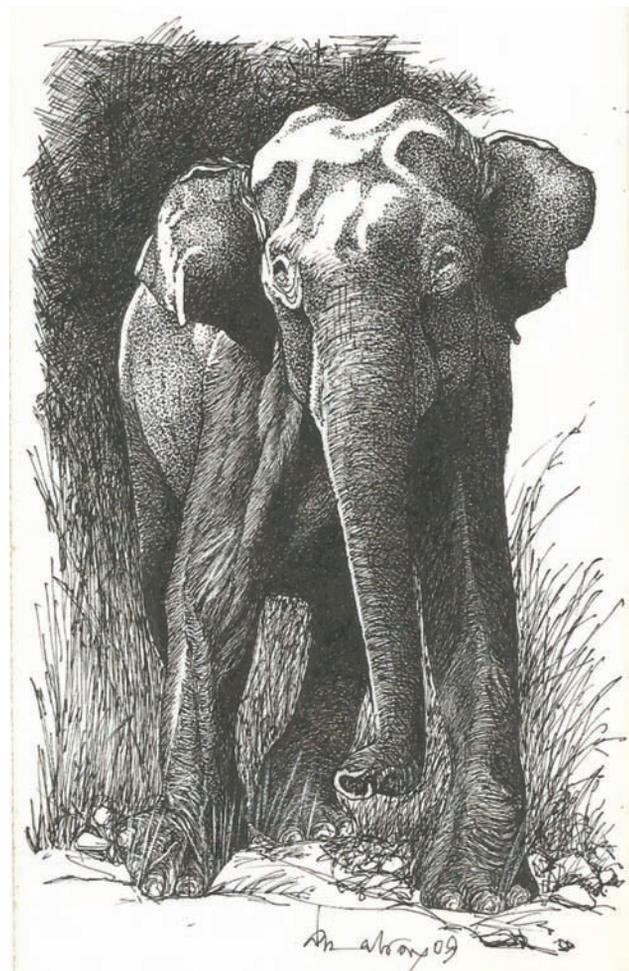
for scientifically accurate information in order to have this discussion. A cross sectional study of people working with elephants is currently being initiated. This study will compare people working with elephants with those who work with other animal species. Tb testing of the people participating in the study will use a new interferon gold test. The first question will simply be to determine if people working with elephants have a positive or negative Tb test. The second question will determine if people working with other animal species have a positive or negative Tb test. The challenge will be matching participants with years of working with elephants, to individuals with years of working with non-elephant species. The Elephant Managers Association (EMA) has offered to be a resource to help identify participants for this study.

Interesting facts about tuberculosis include:

- In all species, tuberculosis as an active infection can only be diagnosed following isolation of the Tb organism through culture techniques. Serology testing alone does not confirm a diagnosis of active Tb.

- When infected, only 3% of humans develop clinical Tb.

- The vast majority of people affected with Tb are not shedding and are not contagious to others, which may be similar in elephants. It also appears probable that elephants have long latent periods in which they are not infective.

- There are currently no reliable liver function tests for elephants. Contrary to most mammals, elephants produce bile alcohols, not bile acids, and liver function tests are based on enzymes for bile acid. Therefore, using these tests in elephants to document liver toxicity from anti-tuberculosis drugs is not possible.

- Targeted animal safety studies are needed to determine the thresholds between Tb drug efficacy and toxicity in elephants.

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Drawing by Arnab Roy