Management and Research Priorities of Tuberculosis for Elephants in Human Care Stakeholders Task Force

American Association of Zoo Veterinarians
Association of Zoos and Aquariums Elephant Taxon Advisory Group
Elephant Managers Association
International Elephant Foundation
Ringling Bros. Center for Elephant Conservation

5 March 2013

Mr. Kevin Shea
Acting Administrator
USDA/APHIS
1400 Independence Avenue, SW
Washington, DC  20250

Re:  Docket No. APHIS-2011-0079; 2006-0044; Guidelines for the Control of Tuberculosis in Elephants

Dear Administrator Shea:

We respectfully submit the following comments on the “GUIDELINES FOR THE CONTROL OF TUBERCULOSIS IN ELEPHANTS 2010” of the United States Animal Health Association (USAHA) Tuberculosis Committee,” (hereinafter, the “2010 Guidelines”) pursuant to the Notice of Availability published in the Federal Register, 78 FR 69078 (January 4, 2013). We strongly urge the Animal Plant and Health Inspection Service (APHIS) of the United States Department of Agriculture (USDA) to NOT accept these proposed 2010 Guidelines.

As explained herein, it is the collective professional opinion of the undersigned that the 2010 Guidelines are not supported by sound science and will not result in the provision of adequate veterinary care for elephants.

The Management and Research Priorities of Tuberculosis for Elephants in Human Care Stakeholders Task Force (hereafter, the “Elephant Care Task Force”), is a group of specialists in
the fields of elephant husbandry, elephant veterinary medicine, elephant management, zoonotic and human infectious disease, public health, and animal sciences that first convened over two years ago to address questions and concerns over the science and data supporting the 2010 Guidelines for the Control of Tuberculosis in Elephants as currently under consideration by the USDA.

The attached document addresses our specific concerns with the content of the 2010 Guidelines. However, in short, we believe that USAHA and USDA have failed to clearly articulate or demonstrate the real risks to animal health, or public and occupational health that the 2010 Guidelines purport to address and, furthermore, that the scope of the guidelines is not consistent with the USDA’s authority under the Animal Welfare Act.

We question the disproportionate reliance on the use of the serological tests as a basis for making important decisions about animal health, treatment, potential exposure risks, and travel restrictions. Additionally, the public policy implications and burdens associated with compliance with the 2010 Guidelines far exceed any demonstrated risk to animal, public, or worker health. They are, therefore, premature at this time.

We urge USDA to continue to refer to the use of the 2008 Guidelines currently in place unless further scientific knowledge is acquired suggesting a change is needed. From a practical viewpoint, USDA’s use of multiple versions of each USAHA revision simultaneously has caused unnecessary confusion for veterinarians, elephant managers, owners, and state agencies, including state veterinarians and public health veterinarians, while doing little to promote actual elephant welfare. In fact, some of these actions have resulted in unnecessary travel restrictions and disruptions to business, while other actions have caused elephants to undergo unnecessary repetitive testing and potentially dangerous drug treatment. None of these further or ensure adequate veterinary care for elephants or compliance with APHIS’ regulations and in some respects the 2010 Guidelines would interfere with such care. Moreover, this particular disease in elephants appears minimally infective, and has a low prevalence in the current captive U.S. elephant population, which raises questions about the appropriateness of the considerable resources devoted to it by APHIS.

USDA licensed elephant holders, many of whom are small facilities, have taken great care and gone to great expense to meet the unwieldy and often illogical provisions and requirements for testing and treatment that APHIS already imposes on them. Zoos, circuses, sanctuaries, and private owners with elephants are dedicated to the welfare of their elephants, and with reasonable
and good science based recommendations can effectively manage this disease and promote the humane and responsible care of their elephants. Unfortunately, the 2010 Guidelines, based on minimal science or real risk, as well as on the use of unpredictable and unproven serological tests, will result in unnecessary and unfair restrictions on the movement of animals in interstate commerce, as well as potentially harmful treatment of healthy animals.

The Elephant Care Task Force finds that the 2010 Guidelines were developed with neither transparency nor participation from key segments of the elephant-holding community. This is troubling given that if the 2010 Guidelines are adopted by APHIS they will directly impact the health and welfare of the more than 400 elephants currently held in USDA licensed facilities including, possibly, euthanasia. Nor was it truly independent from APHIS. The Subcommittee of the USAHA Tuberculosis Committee that created the 2010 Guidelines consisted of six (6) members, one half of who were APHIS employees. The composition of the group was limited with only two members with any direct experience in elephant veterinary care and it excluded most of the original pre-2008 members of the National Tuberculosis Working Group for Zoo and Wildlife Species that had developed all previous versions of the Guidelines. There were no published criteria for Subcommittee membership or its procedures. It held no public meetings and in fact most deliberations took place via email. Additionally, this Subcommittee is chaired by a USDA employee, raising further concerns about agency bias and whether or not requirements for administrative rulemaking including notice and public comment are applicable.¹

In conclusion, the 2010 Guidelines raise serious procedural, public policy, scientific, veterinary and legal issues and should not be adopted since they do not meet the agency’s stated purpose of ensuring adequate veterinary care. Instead, the agency should request USAHA to review the current 2008 Guidelines through a process that:

(a) is more inclusive and provides for participation by elephant veterinarians and other scientific disciplines as well as elephant holding facilities²,
(b) seeks to identify the actual risks that the guidelines purport to address, and
(c) ensures that all available scientific information regarding the risks of infection, transmission, and treatment and the accuracy of screening tests be taken into account.

¹ The Federal Register Notice specifically noted that APHIS was only seeking comments on whether the 2010 Guidelines should be accepted and not on specific provisions thereof, further exacerbating the lack of participation.
² We note that the USAHA Tuberculosis Committee has recently agreed to add several new members to the Subcommittee including representatives of the Elephant Care Task Force.
We appreciate the opportunity to submit these comments and to furthering the cause of ensuring the veterinary care and welfare of all elephants in the United States.

Sincerely,

Tom L. Albert
Vice President, Feld Entertainment and the Ringling Bros. Center for Elephant Conservation
Vice President & Board Member, International Elephant Foundation

Kay A. Backues, DVM, Dipl. ACZM
American Association of Zoo Veterinarians (AAZV) Representative to the Elephant Care Task Force
Director of Animal Health
Senior Staff Veterinarian
Tulsa Zoo

Joan Galvin
Kelley Drye & Warren
On behalf of the Outdoor Amusement Business Association (OABA)

Rob Hunter, MS, PhD,
Scientific Advisor
International Elephant Foundation

David S. Miller, DVM, PhD, Diplomate, ACZM
American Veterinary Medical Association (AVMA) Representative to the Elephant Care Task Force

Deborah Olson
Executive Director
International Elephant Foundation

Heidi Riddle
Elephant Managers Association (EMA) Representative to the Elephant Care Task Force

Dennis Schmitt DVM, PhD, Diplomate ACT
Ringling Bros. Chair of Veterinary Care & Director of Research and Conservation
Alumni Professor of Reproductive Biology
William H. Darr School of Agriculture
Missouri State University

Ellen Wiedner, VMD, DACVIM (Large Animal).

Mark Wilson, DVM
1. Introduction

The Notice states that the agency is proceeding with accepting these USAHA Guidelines as an exercise of its authority to ensure that licensed animals are receiving adequate veterinary care. We agree that animal health and welfare are priority. However, it is the collective professional opinion of the Elephant Care Task Force that the 2010 Guidelines are not supported by sound science and will not result in the provision of adequate veterinary care for elephants.

While tuberculosis is a serious disease that can and does impact the welfare of elephants, experience indicates that it is manageable under the current 2008 Guidelines. This disease is just one of many factors that can affect the welfare of elephants, but elephants can and do receive good humane care in both traveling and stationary facilities. From all reviewed data there are indications this disease in elephants is slow moving, has a low incidence and a low prevalence in the current captive elephant population. (Feldman et al, 2013). We do, however, agree with APHIS’s acknowledgement that the potential presence of TB in some elephants does not constitute a public health issue and, therefore, should not form the basis for regulation by USDA under the AWA.

We believe the Guidelines and the ad hoc process used to develop them are seriously flawed and would result in unnecessary and unfair restrictions on the movement of animals in interstate commerce as well as the unnecessary and in some cases harmful treatment (even possibly destruction) of animals that are not ill and present no serious risk to other animals or the public. Furthermore, the 2010 Guidelines would have a disparate impact on traveling elephant versus stationary exhibitions and such impacts need to be fully considered and justified.

The 2010 Guidelines raise serious procedural, public policy, scientific, veterinary and legal issues and should not be accepted. Instead the agency should request USAHA to revise the Guidelines through a public process that ensures that all appropriate information is considered and appropriate experts from the elephant and veterinary stakeholder community are involved. In this way there is a greater likelihood that the resulting recommendations will be reasonable and appropriate and can be implemented in a manner that truly does serve animal welfare.

2. Definitions

Many of the problems with the 20120 Guidelines stem from the “Definitions” section that contains several provisions that are misleading. Among other things it reflects several significant and seemingly arbitrary departures from the 2008 Guidelines.

It is unclear why this section includes terms that are not used in the body of the text, such as airborne transmission, contact transmission, direct contact transmission, indirect contact transmission, fomite,
incidence, index animal (rather than case or culture), premises, prevalence, rapid test, and spoligotyping. This haphazard approach suggests a lack of clarity regarding the intent of the document and the concepts that are presented, and raises questions about the scholarship used in developing the guidelines. In sum, they create confusion and suggest that the document is not sufficiently grounded to result in improved elephant veterinary care or welfare. In addition, they compromise the potential for developing appropriate performance standards.

Definitions with comments and concerns:

Page 2, ancillary diagnostic test: while this test category is mentioned, the guidelines fail to indicate how they should be used to support the diagnosis. The term is also inconsistently used, such as where the gamma-interferon test is listed as ancillary in this section, but is not listed in section 6.

Page 2, airborne transmission: This definition is one that seems to have been drafted in a manner that is intentionally misleading. While some microorganisms may be dispersed over-long distances by air carriers, there is very little likelihood that *M. tuberculosis* could be transmitted by elephants in such a manner in an outdoor or well ventilated enclosure space. It is possible that this definition refers to the facility in Tennessee where humans and elephants had evidence of *M. tuberculosis* infections (Murphree *et al.*, 2011). However, this study acknowledged incomplete adherence to safety protocols, failed to rule out community exposure of office personnel to *M. tuberculosis*, and the absence of *M. tuberculosis* isolates from humans fails to support the hypothesis that elephants and humans were infected with the same strain, let alone the direction of transmission. This is in contrast to aerosol transmission among humans, even in close quarters such as an airplane, where “only those travelers in close contact with and exposed to the index case for at least 8 hours” are at risk for transmission, where close contact is defined as two rows in front and back of the index case, as well as the row where the index case is seated (World Health Organization, 2008). In addition, the reference to Siegel 2007 is misleading since it specifically described airborne transmission in an enclosed area, not one that is well ventilated, much-less outdoors. References to CDC materials regarding the risks of transmission of *M. tuberculosis* in humans also contradict this broad open-ended approach. Lack of adherence to science-based evidence will not protect human or animal health, as indicated in the Federal register, and USDA fact sheets and news releases.

Page 3, the definitions for direct and indirect contact are misleading and imply that transmission via riding elephants and other activities, as well as via inanimate items, is responsible for transmission of *M. tuberculosis* from elephants to humans. This is one of the most troubling provisions of the whole document since, without any scientific or even anecdotal evidence, it suggests that casual physical contact with an elephant (such as touching or riding an elephant) results in transmission of *M. tuberculosis*. This is just not true and there is little if any chance of contracting *M. tuberculosis* from an elephant ride, or touching an elephant. *M. tuberculosis* has never been shown to be spread from fomite transmission. Furthermore, this is inconsistent with evidence that TB infected elephants are unlikely to shed the organism (Verma-Kumar *et al.*, 2012) and World Health Organization perspectives on transmission of *M. tuberculosis* (World Health Organization, 2011). This also indicates an absence of recognition of the risks of aerosol transmission in confined spaces (which are low) versus the open-air settings where elephants

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3 See attached Fact Sheets from CDC regarding what is necessary for transmission of TB between people, how TB is NOT spread (e.g. direct physical contact) and risk of transmission during air travel.
exist (where risks of transmission are considerably lower). Moreover, these definitions fail to consider differences in occupational and public health risks.

Page 3, definition of exposure: This definition is so broad and ill defined as to be unempirical even though the concept of exposure is relied upon heavily throughout the document. There are no parameters around exposure: how much contact? How far? How often? What kind of contact? Indoor? Outdoor? What role do weather conditions play? In practice it would seem that “exposure” is in the eye of beholder and that what is considered exposure in one case is not in another case with no explanation. Again, never been demonstrated that M. tuberculosis is spread from fomite transmission. The definition of exposure needs to be more performance-based and needs to be scientifically sound.

Page 3, the definition of the Dual Path Platform (DPP) appears to be more of an advertisement for the test, rather than the definition. In addition, the underlying assumption in the written description is that the MAPIA is more accurate than it actually is (see discussion in Section 7).

Page 4, definition of incidence: This definition suggests a fuzzy understanding of the term, and the term is not used subsequently. Why wasn’t a simple definition provided, such as “the number of new cases per unit of time”?

Page 4, incomplete definition of index animals: “in a population” must be added to the end of this definition to be accurate. The text refers to index cases and index cultures, and this should be clarified in the definitions.

Page 4, the definition of infected elephant includes serology as a means for classifying animals as infected. As indicated in Section 7, this definition is not defensible and is inaccurate. This is also the most significant departure from the 2008 guidelines. The 2010 Guidelines define that term, for the first time, to include not just culture positive animals but elephants who have had reactive serological tests, even though that directly contradicts what the agency has always stated: that the culture (trunk wash) is the “gold standard” and the only means of identifying an infected elephant other than on post-mortem exam. If serological tests were conclusive, than there would be no sense in continuing to require cultures for all elephants.

Page 4, the definition of the MultiAntigen Print ImmunoAssay (MAPIA) indicates that it is a confirmatory test for the STAT-PAK. As indicated in the discussion on Section 7, confirmatory tests must be independent of antecedent tests, and the overlap of antigens violates these criteria (Whiting et al., 2003). The persistent repetition of this statement indicates a fundamental lack of familiarity with the principles of clinical epidemiology, and ignorance of these principles invalidates the use of serology as a population screening or diagnostic tool until more accurate assessments are available. The document implies that the STAT-PAK and MAPIA are used as a serial testing procedure, but the absence of clarity on this point or the use of this term suggests a lack of familiarity with the basic principles of validating diagnostic tests. Failure to define and distinguish between diagnostic and screening tests further confirms a poor grasp of the concepts needed to appropriately apply diagnostic tests for tuberculosis to improve animal health and prevent human exposure. On a more practical level, the MAPIA only confirms that the antibody stripe seen on Stat-Pak is repeated and separated out into individual antibody types. As it is the
same methodology, the definition in the Guidelines may create the misconception that this is somehow a different test or result; it only confirms the STAT-PAK, it does not confirm that the animal is infected.

Page 5, the definition of non-reactive is incomplete. Given the detailed explanations provided elsewhere, it is unclear why the clinical implications of non-reactive are not clarified. Is this because the authors are uncertain what it means? This definition seems to have an underlying assumption that non-reactive animals are false-negatives.

Page 6, definition of triple sample method: this definition is unclear. Does it refer to trunk wash samples, as is typically the case? If so, it needs to state this.

Page 6, definitions of sensitivity and specificity: these definitions fail to recognize that these values vary by population and disease prevalence (Leeflang et al., 2009; Dohoo et al., 2003). The failure to include the terms positive predictive value and negative predictive value reinforces the perception throughout the document that standard clinical epidemiological principles were not followed in assessing the accuracy of diagnostic tests or how to appropriately apply tests for the control of disease in a population. The positive and negative predictive values are more appropriate indicators of a test’s accuracy for a specific case (Dohoo et al., 2003).

3. Annual Testing

ElephantTB STAT-PAK® and MAPIA™ Collection Procedure

The requirement for the presence of a USDA veterinarian is extreme and unnecessary. Many other USDA regulated diseases with billion dollar agricultural impact do not require the presence of a USDA veterinarian. This regulation does not explain the difference between the required presence of a USDA veterinarian for the collection of blood samples from elephants as opposed to the Cervid testing guidelines that allow ‘Designated Accredited Veterinarians’ (DAVs) to collect blood samples for the CervidTB Stat-Pak Antibody Test Kit.

4. Culture Collection Procedure

No comments.

5. ElephantTB STAT-PAK® and MAPIA™ Collection Procedure

No comments.

6. Ancillary Diagnostic Tests

It is not clear how ancillary tests are used to support the diagnosis of tuberculosis (as stated in section 2), while the ancillary tests presented in this section are not recommended for use. In addition, gamma-interferon is listed as an ancillary test in Section 2, but is not listed among the currently unavailable tests
in this section. The stakeholders request evidence of the positive and negative predictive values for use of these tests for diagnosis of tuberculosis in elephants.

7. TB Management Groups

This section relies on the ElephantTB STAT-PAK to classify elephants into management groups. Use of this test relies on fallacious interpretations of the test’s accuracy, based on Greenwald et al (Greenwald et al., 2009). Although any study can be criticized, we will restrict our comments to the weaknesses that most seriously compromise the mandated use of these assays, and therefore fail to contribute to strategies for improving elephant or human health.

The Greenwald paper claims, “The serologic assays demonstrated 100% sensitivity and 95 to 100% specificity”. However, this is based on an experimental design where the infected animals either died or were humanely euthanized. This indicates that these animals all had end-stage infections. Consequently, this study does not include data from earlier-stage animals that this test was intended to identify. Failure to include the subjects of interest is a basic experimental design flaw. Furthermore, it is well recognized in the medical sciences that failure to include the full-spectrum of disease states results in substantive overestimations of test accuracy (Lijmer et al., 1999; Rutjes et al., 2006). This weakness is magnified by the small sample size of infected animals. Based on humans and other species, it is more precise to believe that a more representative study would result in substantially lower estimates of test accuracy. There is also the concern for industry-derived bias in the data that has been published. In comparison with serology for TB in humans, the World Health Organization indicates that “…commercial serological tests provide inconsistent and imprecise results with highly variable values for sensitivity and specificity, and high proportions of false-negative and false-positive results. There was no evidence that existing commercial serological assays improve outcomes.” (Page 55) (World Health Organization, 2011). For comparison, the Stat-Pak only identified 64% of TB infected lions (Miller et al., 2012) and had a test sensitivity of 87% in cervids (Nelson et al., 2012) under field conditions where the infection status was established at necropsy and the sample was less biased towards chronic, end-stage infections. Furthermore, solely depending on a test’s estimated sensitivity and specificity without an understanding of the population is not consistent with current medical standards; appropriate interpretation of a diagnostic assay requires knowledge of the prevalence of disease in a population (Leeflang et al., 2009; Dohoo et al., 2003), and there is no evidence available indicating that this has been considered. This was recognized in Bontekoning (2009), where an assessment independent of the manufacturer documented a STAT-PAK sensitivity of 80%, specificity of 87.23%, and a positive predictive value of 57.14%, which is close to the odds of flipping a coin.

The Greenwald paper indicates that it has demonstrated a proof-of-concept for their assays. However, the manufacturer’s knowledge of how to go beyond proof-of-concept and correctly validate and apply these tests is lacking. For instance, the 2010 Guidelines require testing by the Stat-Pak followed by confirmation with the MAPIA/DPP and this is apparently USDA policy (Sofranko, 2011). Besides the absence of data supporting the use of these assays for either serial or parallel testing, it is well established that confirmatory tests must be independent (Whiting et al., 2003), and the overlap of antigens among these assays violates this basic principle (Table 1). Furthermore, the inconsistency in antigens that are reported for the MAPIA varies between the Methods, Table 2, and Figures 2 and 6 in Greenwald.
(Greenwald et al., 2009), suggesting that there is selective or incomplete reporting, which compromises objective assessments of the study and potential for generalizing results (Chan et al., 2004; Vandenbroucke et al., 2007). Selective reporting, bias, and a lack of knowledge of the principles of clinical epidemiology are particularly egregious in a recent publication (Lyashchenko et al., 2012) where the manufacture concludes in the last paragraph that their tests were “confirmed to have a high predictive value”, when they failed to state whether they were discussing positive or negative predictive values, could not calculate positive or negative predictive value from the data that was presented, had not previously mentioned test predictive value in the manuscript, and could not calculate any measures of test accuracy (including test sensitivity and specificity) from the data that was selectively presented in this case report. This error was also present in Greenwald, et al, 2009.

**Table 1. Comparison of proteins used in MAPIA, Stat-Pak, and DPP assays**

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The inferences possible from Greenwald’s small sample size of infected animals are further limited by the joint analysis of two different genera of host species (Loxodonta and Elephas; an unstated assumption that these two genera have equivalent host responses without any supporting data); two different organisms (M. tuberculosis and M. bovis; an unstated assumption that these two organisms are equivalent antigens, without any supporting data); two different culture sampling methods (postmortem cultures and ante mortem trunk washes, which the author’s acknowledge as not being equivalent gold standards); multiple populations of elephants (unstated assumption that all elephant populations had similar exposure to mycobacterium without even a citation of support). Inferences possible from the small sample size are further limited by the author’s acknowledgement of variable responses to tubercular organisms among different elephants. Additional substantive problems with the manuscript include an artificially increased estimate of seroprevalence because “The TB-exposed group was considered only for seroprevalence analysis”; justification of false-positive results as being associated with arthritis without presenting all of the clinical data that was available to the authors; temporal data from selected infected animals was presented without comparison with noninfected animals; use of different methodologies to read the DPP without data supporting their equivalence. Intermixing of data appropriate for either the Discussion OR the Results sections; vague study objectives listed in the Introduction; and the hybrid mix of proof-of-concept studies extended to inappropriate population-level inferences further contributes to an impression of a loose conglomeration of data from which little legitimate inference can be drawn, other than that this is preliminary data, and further data may support the value of these assays as screening or diagnostic tests. This is in marked contrast to the USAHA 2010 Guidelines where it is incorrectly indicated that the Statpak and MAPIA are valid screening and confirmatory assays, respectively.

An additional concern is the close association of the manufacturer with USDA personnel. While we applaud collaborative efforts, this close association appears to have confounded USDA’s ability to objectively assess the diagnostic accuracy of these assays. In particular, mandated use of an industry partner’s diagnostic test where hundreds of dollars are charged for testing raises questions of propriety. This conflict of interest is a well-recognized concern in the biomedical sciences and public health policy (Meffert, 2009; Lundh et al., 2012). This concern for inappropriate relationships is reinforced by initial USDA requirements that the laboratory provide results only to the USDA and not the elephant’s owner or attending veterinarian, and the Guidelines current lack of clarity on who receives the data.

With regards to the specifics of this section, as indicated above, use of serology and assumptions that the tests have near 100% accuracy is not science-based policy, and similar comments apply to the various temporal and quarantine restrictions that were listed in this section. The establishment of classifications and management responses based on serology is also not legally defensible when it is acknowledged on page 32 of the 2010 Guidelines that “A positive culture of M. tuberculosis is, therefore, the only diagnostic test result used as a basis for making decisions in the guidelines”. Requiring these serological tests for movement of elephants will also interrupt elephant conservation when the test is not available, as is currently occurring, and this is counter to all other USDA policies for movement of animals that are much higher risks for importing and transporting contagious infectious diseases. In addition, the frequency of testing has not been documented as a science-based policy with known costs and benefits. Furthermore, failure to include management guidance for culture-positive, serology negative animals (which the USDA should be aware of) indicates an absence of due consideration for practical, real-world situations, as well as failure to recognize that the serologic assays are not 100% accurate. The provisions
for therapy in this section are similarly weak in the absence of consideration for real-world situations, by advocating for tests of liver function that are not valid for elephants, are not evidence-based, mandate arbitrary treatment protocols and durations, and fail to provide guidance for the appropriate response within the regulatory framework when toxic side-effects from treatment are evident. This is wholly inconsistent with USDA’s stated purpose of ensuring adequate veterinary care.

Elephants that are trunk wash positive are accepted by all as potential sources of infection for humans and other animals, and restrictions on these confirmed cases are reasonable. However, current evidence indicates that the vast majority of elephants that are serologically reactive are asymptomatic, and unlikely to shed mycobacterium (Verma-Kumar et al., 2012). This is consistent with previous communications to a USDA and USAHA representative that elephants do not pose substantial risks to humans (National Association of State Public Health Veterinarians, unpublished letter to Janet Payeur, June 28, 2012) (Attached), and are a virtually nonexistent risk to livestock. Because treatment can result in severe side effects and compromised animal health, there is a need for a comprehensive analysis that objectively assesses the various demerits and benefits of various testing and treatment options for tuberculosis in elephants. This assessment must include more accurate assessment of the serologic assays and how they are appropriately interpreted in populations and for clinical applications prior to requiring their use.

Given the above, the Elephant Care Task Force believes that the groups established by the USAHA Elephant Tuberculosis Subcommittee are invalid. Nevertheless, we offer additional comments on the TB Management Groups:

**GROUP 2: Culture negative; ElephantTB STAT-PAK® non-reactive; exposure to culture positive animal within the last 12 months.** Again this requires a more specific definition of what constitutes “exposure” as it contains no parameters of time or space or distance. This is important since it is well documented that M. tuberculosis has low infectivity in elephants and humans. A 3-year period of increased testing is excessive and unnecessary. While the exact time to sero-conversion is unknown, never has sero-conversion been documented to take 3 years in any animal. Consequently absence of a defined exposure history is problematic.

**GROUP 3: Culture negative; ElephantTB STAT-PAK® reactive**

It is required that blood from elephants with reactive ElephantTB STAT-PAK® results be submitted for MAPIA™/DPP® testing (see item 5 above). Based on MAPIA™/DPP® results and exposure history, the elephant will fall into one of the following subgroups:

**A. Culture negative; STAT-PAK® reactive, MAPIA™/DPP® non-reactive, no known exposure.** This should be considered a Negative elephant w/o any history of exposure and the need for increased culture should be the same as the non-reactive exposed elephant in #2.

**B. Culture negative; STAT-PAK® reactive, MAPIA™/DPP® non-reactive, known exposure to TB culture positive elephant (no time limit on exposure history).** From other species/diseases we can infer that antibodies develop within days or weeks. The requirement to continually repeat the MAPIA/DPP every 6 months is an unnecessary financial burden that does nothing but help Chembio’s financial rating.
**C. Culture negative; STAT-PAK® reactive, MAPIA™/DPP® reactive, no known exposure.**

There is no reason to treat these animal any different than Group 2A as without a history of exposure the MAPIA/DPP only confirms that the stripes are there. As we have indicated, reactive MAPIA/DPP is not equivalent to positive exposure.

Without a history of exposure there is no need for a travel restriction if increased surveillance is implemented. The concept of latency should be considered here and that the animal may have been infected and will never develop disease or shed, or that it could develop disease one day. The focus should be on the health of the animal, monitoring body weights, increased trunk wash cultures. An additional issue is that restrictions **MAY** be lifted if approved treatment –Is that not true of all treatment? What does **MAY** mean? This is just one example in which the 2010 Guidelines, which are said not to be a product of USDA, are later going to be construed and applied by USDA. Yet there is no explanation of the standards or even the process that USDA will follow in taking (or not taking) actions.

**D. Culture negative; STAT-PAK® reactive, MAPIA™/DPP® reactive, known exposure to TB culture positive elephant (no time limit on exposure history).** While continuing increased trunk washes for this group for some time seems appropriate, there is no justification for imposing the costs and burdens of increased serological testing. There is a need to focus facility resources on trunk washes, maybe even every 3 months for 2-3 years, which in itself is not cheap but much more. Antibodies would not respond quickly to changes and wouldn’t change if the animal were already infected and then began shedding. Consequently there is nothing of clinical significance that the MAPIA/DPP (+) reaction that will show us of an animal that is already reactive. MAPIA/DPP changes could only become negative so what does that mean? That the animal has overcome infection? If culture status changes to (+) then we have our most important answer and this is where we should focus the USDA’s and the relevant institution’s efforts and resources.

8. **Principles of Anti-tuberculosis Therapy**

   See comments in section 11.

9. **Anti-tuberculosis Drugs**

   See comments in section 11.

10. **Dosages and Routes of Administration**

    See comments in section 11.
11. Blood Levels

Antimicrobial Breakpoint Interpretation in Zoological Medicine

Global events and perceptions regarding the use of antimicrobial agents in animals have placed even more importance on the essential role of antimicrobial susceptibility testing of bacteria isolates from animals. However, little information is available on microorganism/antimicrobial/host interactions with zoo species. Currently, veterinary-specific breakpoints have been compiled and published in the Clinical Laboratory Standards Institute’s (CLSI) M31-A3 (CLSI, 2008a). Also in this document is published the criteria for several antimicrobial agents that are commonly used in veterinary medicine yet do not have veterinary species-specific breakpoints. The number of drugs in the latter category gets smaller with each revision, but even the veterinary-specific criteria must be interpreted with caution when applied to zoological species for treatment considerations and therapy.

The first reason for this caution is how the breakpoints are determined by the Veterinary Antimicrobial Susceptibility Testing subcommittee. The path for breakpoint determination is outlined in the CLSI M37-A3 document “Development of in vitro susceptibility testing criteria and quality control parameters for veterinary antimicrobial agents.” (CLSI, 2008b) This document outlines the pathway for antimicrobial agents for the setting and recommendation of veterinary-specific clinical breakpoints. “S” is the susceptible interpretive test category implying that the infection due to the isolate may be effectively treated with the normal dosage regimen of an antimicrobial agent recommended for that type of infection and causative bacterial species. This is the fundamental piece of information that is often not understood by the attending zoo veterinarian. The recorded results indicate that the isolate is “S/I/R” for the culture submitted when tested against the diagnostic lab’s standard array of antimicrobial agents. The S/I/R are reported using the information provided in the M31-A3 previously mentioned. The reporting institution does not know, in the vast majority of cases, the host species, route of administration, or pharmacokinetics of the antimicrobial agent being evaluated and reported. They only have two pieces of the puzzle: microorganism and class representative antimicrobial agent tested.

Most veterinarians then make the assumption that if the microorganism is S, then they simply treat with that agent and positive results will follow. Antimicrobial susceptibility testing of bacteria of animal origin ultimately is intended for the selection of antimicrobial agents for better clinical outcome. The premise of veterinary antimicrobial susceptibility testing (VAST) is that in vitro test results can be used to guide the veterinarian in antimicrobial drug therapeutic decision-making, when the testing is performed in a standardized and reproducible manner. Just as important, clinicians must understand that antimicrobial resistance is not necessarily an inherent or absolute characteristic of bacteria, but rather that resistance indicates the crossing of a threshold.

Although “S” and “R” are usually considered binary characteristics, in fact, resistance can only be identified if a clinical breakpoint or threshold of antimicrobial concentration is pre-determined and agreed-upon by regulatory agencies and standard-setting organizations such as the Clinical and Laboratory Standards Institute. The threshold (“interpretive criterion”) cannot be arbitrarily determined (e.g., by saying that all bacteria with a zone of inhibition of less than “X” mm are resistant) but must be validated with the appropriate data including knowledge of concentrations of antimicrobial drug that can
be achieved in an animal (pharmacokinetics), the best presentation of the drug to the bacteria in the host (pharmacodynamics), range of concentrations of antimicrobial drug required to inhibit growth of populations of wild-type bacterial pathogens, and clinical outcome of treatment of the pathogen with approved or commonly accepted doses of antimicrobial drug. It goes without saying that the determination of S is a complex process for the indication(s) on the product label. Attempting to determine this value for each and every “bug/drug/species” combination in zoological medicine would an astronomical undertaking.

To avoid misinterpretation, CLSI M31-A3 recommends that diagnostic laboratories only test and report breakpoints for agents appropriate for therapeutic or control use. Agents could be added based on specific therapeutic needs (such as for specific zoological species where a specific agent and formulation are commonly used). Given the limited number of antimicrobial agents approved for use in some animal species, “extra-label” use of antimicrobial agents is commonly practiced. The U.S. Congress, in the Animal Medicinal Drug Use Clarification Act (AMDUCA), has defined extra-label use as the “actual use or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling.” This includes, but is not limited to: use in species or for indications (disease or conditions) not listed in the labeling; use at a dosage level higher than those stated in the label; and use of routes of administration other than those stated in the labeling.” This type of use has regulatory acceptance in many countries (e.g., extra-label use permitted under the AMDUCA regulations). While laboratory personnel should be familiar with extra-label use of antimicrobial agents in animals, the laboratory client is responsible for using the compound appropriately in the animal.

The laboratory client is also responsible for using the agent appropriately for the various animal types or categories (e.g., calves, lactating dairy cattle). The laboratory client assumes all responsibility for efficacy, safety, and residue avoidance with extra-label uses of antimicrobial agents. The laboratory should be prepared to offer advice to the veterinarian to enable appropriate decision-making. Although the laboratory may choose to modify the list of antimicrobial agents it tests and reports, on the basis of public health concerns, it needs to be done in consultation with appropriate experts, based on good clinical judgment, and in accordance with recognized principles of judicious use. Veterinarians working with minor or zoological species should make themselves aware of the tables provided in M31-A3 so as to understand what the breakpoints are and what bug/drug/species indications they are based on.

Numerous antibiotics are approved for use in different animal species by the U.S. Food and Drug Administration’s Center for Veterinary Medicine (“FDA-CVM”) or comparable regulatory authorities in other countries. Factors such as microbiological activity, clinical efficacy, and pharmacology should be considered for therapy, indications, and restrictions. CLSI document M31-A3 lists compounds in groups in which drugs are approved for use in the indicated animal species by the US FDA-CVM (Groups A, B, C, and D). It is most appropriate to report those antibiotics that have veterinary-specific interpretive criteria over those using human interpretive criteria (Group A). These antibiotics have demonstrated an acceptable correlation between in vitro susceptibility test results and clinical criteria outlined in M37-A3. While antimicrobials evaluated using human interpretive guidelines (Group B) may perform adequately in diseased animals, the interpretive relationship for veterinary applications has not been determined. Some antimicrobials are FDA-CVM approved for use in a specific animal species but have neither veterinary-specific nor human-specific interpretive criteria (Group C) and reporting interpretive criteria from one
animal species to another (extra-label use, Group D) is not recommended due to various differences in dosages and pharmacokinetics.

If the generated VAST data are likely to be used to make clinical treatment recommendations for bacterial diseases in animals, antimicrobial drug selection should include, when available, drugs approved for the indication and animal species, and might also include drugs approved for other indications in the same animal species. In some cases, but typically not zoological medicine, the use of commercially available panels of antimicrobial agents for use in VAST is a simple choice, since the panels have generally been selected with drug approvals and common usage in mind. Zoological medicine is an important and serious exception to this.

**Intra- and Interspecies Dose Extrapolation**

Species differences in drug absorption, distribution, metabolism, and excretion (ADME) for numerous pharmaceutical agents have been well documented for domestic species; however, there is limited information concerning the ADME of drugs in nondomestic species (Hunter, 2009). Lack of approved pharmaceutical agents and/or pharmacokinetic data in the literature for zoo species is a major issue for veterinarians attempting to treat these animals. Zoological medicine practitioners take approved agents (veterinary or human) and extrapolate their use to non-approved species. The range of animals a zoo veterinarian cares for varies from very small invertebrates (honeybees) to mega vertebrates such as elephants and whales. The decision on dose, duration, and treatment interval is often made with limited species-specific (pharmacokinetic and/or efficacy) information. Because of the monetary value of these animals or their status as endangered species, the method of “trial and error” for antimicrobial dosage selection is inappropriate.

In zoological medicine, various methods have been used in an attempt to extrapolate or predict safe and effective dosage regimens (Hunter & Isaza, 2008). The simplest and typical method of extrapolating a dosage to a nondomestic species is to use a mg/kg dose established for another domestic species or humans. However, this calculation results in a linear increase in the amount of drug administered as body weight increases. Although common, this method tends to overdose large animals and underdose small animals. A second method is similar, except that it takes the approved dose in a specific species and makes an additional assumption that links the dosage to a physiologic function or anatomic feature. Examples are the use of basal metabolic rate or body-surface area as the basis for dosage extrapolation. Allometric scaling of pharmacokinetic parameters is the final method of dosage extrapolation between species. This is commonly used in the pharmaceutical industry to establish the first dosage in human drug investigations. Adaptation of this method for zoological medicine is believed to enhance the ability to estimate therapeutic dosages for nondomestic species. However, relatively recent data (Hunter et al., 2008; Mahmood et al., 2006; Martinez et al., 2006) question the practical use of this approach.

Allometric scaling of pharmaceuticals to predict pharmacokinetics in zoo/exotic animals has considerable benefit for zoological veterinarians. This tool, when used appropriately, can provide an estimate for designing dosage regimens. The example of differences in ketoprofen inversion across species emphasizes the need to understand and be aware of the assumptions when designing treatment regimens based on allometric scaling data. Just as mammals can range from a few grams to thousands of
kilograms, reptiles and birds can also vary in body weight across a wide range. It has been suggested that it is impossible to derive a single equation correlating body mass to metabolic rate for all 6,000 species of reptiles (Funk, 2000). Without knowledge as to the extent and route of elimination of an administered pharmaceutical agent, extrapolation of dosage regimens from one class to another is difficult, if not impossible, with any certainty.

Before extrapolation of any drug dose, the veterinarian should appreciate not only the mathematical assumptions but also the limitations that are associated with allometry. Careful consideration of the available literature to understand the route of elimination and the extent of metabolism of therapeutic agents will greatly assist in determining allometric relationships of pharmacokinetic parameters. There is a continuing need to consider and apply methods for reducing the size and risk of extrapolation error, as this can affect both target animal safety and therapeutic response. Data from at least one large animal (nonhuman and a body weight >70 kg) should be included to reduce potential error (Mahmood et al., 2006).

A Practical Example of Allometry and Breakpoints

The use of the 2010 Guidelines susceptibility testing and the treatment of this bacterial disease in elephants is an example of how the above information can be interpreted and potentially misused. Unlike cattle and other livestock, which are more apt to be infected with M. bovis and are euthanized if positive, in the United States, elephants are recognized for their rarity and value and are treated rather than culled. Mandatory testing and treatment of elephants with TB is overseen by USDA, and the 2010 Guidelines (as well as previous versions) include the subject provisions regarding for drug administration in pachyderms that have been derived from those established for humans. Susceptibility testing for this pathogen is described in detail, for human isolates, in the CLSI M24-A2 document (CLSI, 2011). Using the human pharmacokinetics of the primary antituberculous drugs, the results of in vitro susceptibility testing of these agents appears to correlate well with the clinical effectiveness of these agents in human patients. The interpretive criteria, or breakpoints, are provided in Table 1.

In elephants, the antituberculous drugs differ significantly regarding their pharmacodynamics and pharmacokinetics in humans. In addition, the metabolic state of Mycobacterium tuberculosis significantly affects its susceptibility to antimicrobials. Optimization of dosage of antituberculous drugs is necessary to achieve maximum drug exposure at the site of infection in order to maximize reduction in Mycobacterium tuberculosis viable organisms and to minimize the emergence and selection of resistance (de Steenwinkel et al., 2010).
Table 1. Breakpoints for select anti-tuberculous drugs used in elephants.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Breakpoint concentration (µg/mL)</th>
<th>7H10 agar</th>
<th>7H11 agar</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>0.2</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td>5.0</td>
<td>7.5</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>10&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NR&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>1.0</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>2.0</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>2.0</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

NR=not recommended; ND=not determined. Where multiple values are provided, the second is when resistance has occurred and the drugs are used as “second-line therapies” (modified from M24-A2; CLSI, 2011).

There are published reports on the “population” pharmacokinetics of several antituberculous drugs in African and/or Asian elephants which were used to develop the multi-drug treatment protocols for elephants published in the USDA Elephant TB Guidelines, and were modeled after human disease (Peloquin et al., 2006)). The issues with these types of extrapolation have been previously discussed (Hunter & Isaza, 2008). Using the human breakpoints for isoniazid from the M24-A2 and the plasma concentrations reported by Maslow et al. (2005) one could conclude that the likelihood for efficacy is high with all reported concentrations >0.2 µg/mL for the doses and routes of administration evaluated, but many concentrations were greater than 5×, which seems excessive and could be contributing to the adverse events reported by some clinicians (Isaza, personal communication). Maslow’s group (2005) suggests that area under the curve (AUC) may be the driving pharmacodynamic parameter, which is not surprising given the slow growth of the target pathogen, but the target PK/PD relationship is currently unknown in either elephant species, and is very likely to be different than that reported for humans. This idea is further supported when the fluoroquinolones are evaluated. While in human medicine an AUC/MIC ratio of ≥125 for fluoroquinolones has been shown to eradicate a particular bacterial disease, this ratio cannot be directly extrapolated across species, indication, or pathogen, nor has it been determined for antituberculous drugs. The effective AUC:MIC ratio has been reported to be different between species (Aliabadi et al., 2003). Opinions also differ within the human literature, where some report that a ratio >25 is best, while others state that the ratio must be greater than 350 (Barger et al., 2003). This is complicated by the fact that for the fluoroquinolone ciprofloxacin, 100% of successfully treated patients had an AUC:MIC ratio >3.6 (Barger et al., 2003). It should be remembered that the in vivo antimicrobial effect is the result of dynamic exposure of the pathogen to the antimicrobial and the host immune system (Mueller et al., 2004). The comments and issues raised here also apply to rifampin (Peloquin et al., 2006) and ethambutol (Maslow et al., 2005).
Unfortunately, numerous serious side effects have occurred in the majority of elephants undergoing treatment; 87.5% of elephants were documented to have “one or more side effects... severe enough to warrant temporary discontinuation of treatment” (Weidner and Schmitt, 2007). In many cases, these were severe enough that treatment needed to be discontinued, at least temporarily. Reported adverse effects include anorexia, depression, diarrhea, kidney and liver insults, blepharospasm, and death. The high incidence of severe side effects suggests that the doses of drugs required to achieve human serum levels, may, in fact, be toxic to elephants. This suggests that the treatment provisions within the 2010 Guidelines could actually be harmful to elephant welfare and that USDA adoption of them would not ensure the provision of adequate veterinary care.

12. Postmortem Examination

No comments.

13. Employee Safety and Health

Page 25: We agree that employee health and minimizing transmission of infectious organisms is a concern. We also agree that employees shedding *M. tuberculosis* or *M. bovis* are a risk, and that such employees’ health needs should be addressed. However we have concerns with the following:

Inappropriate recommendations for treatment of humans with evidence of TB exposure:

Page 25: “It is recommended that health care providers who manifest a positive PPD receive INH prophylaxis unless there is a contraindication to treatment.”

a. It is not clear what “health care providers” means. On the assumption that this refers to elephant caretakers, this statement is contradicted by the American Thoracic Society’s most recent published guidelines (cited by the authors) for treatment of active, culture-negative pulmonary tuberculosis, and inactive tuberculosis; treatment solely with INH is only one of three possible therapeutic options for “initial culture negative, no change in CXR” individuals, and is not an option for any other scenarios (Anonymous, 2003):
i. The recommendations for INH prophylaxis are also not apparent in the latest recommendations of the World Health Organization (World Health Organization, 2010)

ii. There is subsequent discussion of interpretation of positive skin tests in humans, with and without prior inoculation with BCG

b. These recommendations for treatment and interpretation of diagnostics are the purview of human medicine, rather than veterinarians and animal health agencies. This is in violation of state veterinary practice acts, and this concern is furthered by recommendations that are counter to the American Thoracic Society and World Health Organization.

Page 25: “Employees with acid-fast positive sputum smears should be removed from animal contact”. While we agree that this is generally a reasonable precaution, the wording suggests a mandate that is applicable to all circumstances. It does not appear to provide leeway for healthy caretakers to wear N95 HEPA filtered masks while caring for animals, even if the absence of an affected caretaker will have an adverse impact on animal health. There are likely additional circumstances where wording that emphasizes a consideration of the risks and efforts to minimize transmission are more appropriate than the existing mandate.

Pages 25 and 26: Failure to cite directly cite Davis, 2001 (Davis, 2001) in this section, while citing a safety reference for laboratories, suggests that the authors have little familiarity with the practical considerations of managing animals that are infected with *M. tuberculosis* or *M. bovis*. Of particular concern is the absence of reference to appropriate disinfectants for mycobacterial agents, and the apparent incorrect assumption that all disinfectants are equivalent. Referring inquiries to local public health departments is unlikely to result in recommendations that are appropriate for animal and human risks, and is consistent with the impression that the authors have little expertise in preventing transmission of tuberculous organisms to humans or other animals.

Page 26: “No specific precautions are necessary for animals that are culture positive for mycobacteria other than *M. tuberculosis* and *M. bovis.*” This is a broad statement that does not recognize that non-
tuberculous mycobacteria are potential environmentally transmitted pathogens (Feazel et al., 2009), and risks misinterpretation, particularly for immunocompromised (pregnant or receiving chemotherapy) individuals. While the risk is low, this language should be deleted.

As a practical matter, this section fails to provide appropriate guidance for protecting human health or transmission to humans or other elephants. Of particular concern is that the authors did not appear to be familiar with the content of the references that were cited where human health risks were concerned. The document’s recommendations on treatment of humans are not consistent with state veterinary practice acts and professional ethics, and contrast American Thoracic Society recommendations that the author’s cite, as well as World Health Organization guidelines. In sum, this section needs to be substantially revised to be: effective at minimizing transmission of infectious organisms to humans and other animals; accurate; and to minimize legal liability for all veterinary professionals and holders of elephants. It is a serious significant and fatal flaw that this section of the 2010 Guidelines does not reflect the level of knowledge and judgment that is expected of an authoritative policy and scientific document that has human and animal health and regulatory implications.

14. Reporting

No comments

15. Appendices

No comments
Annex I: Literature Cited in the Stakeholder’s Comments


Bontekoning, I., Tuberculosis detection in the Asian elephant (Elephas maximus) population of Thailand. 1. Development of an IFN-gamma assay 2. Evaluation of a multiple antigen iELISA and a commercial rapid test. 1-29. 2009. Utrecht University, Utrecht, Thailand: Kasetsart University, Bangkok Chiang Mai University, Chiang Mai.


Ref Type: Conference Proceeding


June 28, 2012

Janet B. Payeur DVM, MPH, PhD
Chair, USAHA Elephant Tuberculosis Subcommittee
Scientific Outreach Coordinator
National Veterinary Services Laboratories
1920 Dayton Avenue
Ames, IA 50010

Dear Dr. Payeur:

On behalf of the National Association of State Public Health Veterinarians (NASPHV), I am providing summary comments on the April 2012 Draft Revision of Guidelines for the Control of Tuberculosis in Elephants. These comments represent a compilation of concerns and requests from a subcommittee of members, who share a particular interest and public health experience in responding to tuberculosis in elephants.

1) Description under airborne transmission: Comments received from tuberculosis control physicians in two separate state health departments expressed concerns about the inclusion of the sentence, "Microorganisms ... may be dispersed over long distances by air currents and may be inhaled by susceptible individuals who have not had face-to-face contact with (or been in close proximity to) the infectious animal or person (Siegel 2007). The likelihood of a person (or animal) to inhale a sufficient dose of Mycobacterium tuberculosis carried by wind currents in an outdoor space, or semi-open well ventilated enclosure is deemed to have extremely rare potential for an exposure to occur. This description in the Guidelines needs to qualify that airborne transmission can occur in closed spaces with a shared ventilation system that may communicate with animal areas and areas housing or office personnel. The Siegel reference is describing airborne transmission in an enclosed area, not one that is ventilated to outside air.

2) Definition of public contact: The current definition, i.e., “any situation”, is too broad to be applied for the purposes of classifying potential human exposures and managing risk of zoonotic transmission. We request that the definition be modified to reflect what is known about zoonotic transmission rather than to be ultra-conservative and cause unwarranted fear or concerns. What is known is that the greatest risk of spread of Mycobacterium tuberculosis from an infectious elephant to a human requires frequent exposures within close proximity to an infectious elephant, or sharing of a common airspace in an enclosed area under conditions of repetitive aerosolization of droplet nuclei (reported in RID 2011;17:366-371). Brief, incidental contact in or around an infected elephant would not likely result in an exposure; nor would just touching an elephant. The scientific evidence for fomite transmission to a person also needs to be presented if included in this definition as a potential route of exposure.
Similar to what is provided in section #13, we suggest added language in the definition of public contact that states something on the order of: “Consult with the State Public Health Veterinarian or State Epidemiologist in your state to obtain guidance regarding the public health risks an infected elephant may pose to the general public as the particular circumstances involving a TB-infected elephant are variable.”

3) Page 10, Group 2: Request adding more detail on what is defined as “cessation of exposure”. For previously culture and STAT-PAK negative elephants in a herd with a culture positive elephant undergoing treatment, we assume exposure cessation has occurred six months after the TB-infected elephant has been undergoing approved anti-tuberculosis treatment, or six months following effective isolation of the TB-infected elephant, or six months following removal of the TB-infected elephant from the premises. If the subcommittee is in agreement with these parameters, they need to be clearly stated in the Guidelines.

What is the basis for the added 6 month travel/public contact restriction (as compared to 2010 Guidelines) for elephants in Group 2? This restriction seems appropriate for travel that would involve change in ownership, i.e. relocation to a new facility/ herd, but seems unnecessary for performing elephants. Since M. tuberculosis has a latency period, and travelling elephants do not typically come in contact with those outside of their herd or come into frequent direct contact with the public, this addition appears to be over restrictive and should be more granular (and science-based) to types of travel. Elephants in this group would be very unlikely to pose a risk of zoonotic transmission to the general public.

4) Request insertion of a small paragraph towards the end of Section #7, TB Management Groups 1-4 (page 15): NASPHV requests consideration of some added language to the Guidelines that addresses working with local and/or state public health officials in assessing public health and occupational health risks associated with a particular elephant. Proposed language -- “Facilities who maintain elephants falling into Groups 2-4 should be prepared to share information, including but not limited to, employee TB status and TB risk factors, elephant medical history, elephant housing and activities with public health officials in order to assist in any assessment or contact investigation associated with the public health risk of an elephant(s).

5) Page 17, section #3, Group 4 elephants: This section is written from the perspective that the STAT-PAK and MAPIA tests are 100% sensitive and specific for elephants that are infected with M. tuberculosis. We know of elephants that have been M. tb culture positive, but negative upon subsequent and repeated STAT-PAK and MAPIA testing. This needs to be addressed for Group 4 elephants. It is an unnecessary expense to the elephant owner to continue to require the serological testing once it is well demonstrated that the individual culture positive animal is non-reactive on these tests, and the MAPIA test will have no value in assessing successful treatment status or recrudescence of infection.

6) Page 18, Section B, Quarantine without treatment: We recognize there is limited data available on the “M. tb elephant-to-elephant transmission range” whether by aerosol transmission or theoretical contact transmission; however, USDA in collaboration with USDA must develop a beginning standard distance between a culture positive elephant and other
elephants for these guidelines to be operational. Simply stating, “Quarantined elephants should be kept out of range from non-infected animals...” is insufficient. Would 100+ yards (> 300 feet) be considered “out of range”, > 150 yards?

7) Page 18, Section C, Euthanasia: Suggest clarifying “...showing clinical signs... Consider changing to .....showing clinical signs of progressive and active tuberculosis disease.

8) Page 21, 23, 25: Terms C_max and T_max are used in the pharmacology sections, but are not defined in Section 2 - Definitions. Suggest adding to definitions before citing in Guidelines.

9) Page 26, Section 12, Postmortem Examination: “It is essential that a post-mortem examination be performed on all elephants that die.” Our reviewers requested clarification – does this refer to all elephants regardless of Group 1-4 status, or just elephants that die while being treated for tuberculosis?

10) Page 28, Section 14, Reporting: Although we are in agreement that all positive M. tb culture results in elephants should be reported to the State Veterinarian and State Health Department, it is not a correct statement in the Guidelines to simply state, “Tuberculosis is a reportable disease.” Disease reporting laws are determined by the individual states. We know that in some states only tuberculosis in livestock animals is required to be reported to the State Veterinarian. Since elephants are not livestock, they are not captured by this reporting requirement in many states. Tuberculosis in humans is reportable to the respective state health department; however, very few states have disease reporting laws that require reporting of tuberculosis in animals to the public health agency. Based on discussions that occurred at a national stakeholders meeting in Fort Worth, TX, in August 2011, there appears to be a misunderstanding among USDA and other elephant-centered organizations about this existing gap in reporting of tuberculosis in elephants.

List of Minor Edits (typographical, formatting, etc.)
Page 3, first paragraph: remove space from NASPHV reference
Page 3, Culture positive contact: ...for M. tb (insert space, add “b”) complex
Page 5, M. tb and M. tb complex: Add space between M and tb
Page 11, bulleted footnote under Group 2: Remove bullet; appropriately place footnote – seems out of place and a little difficult to put into context.
Page 11-14, Follow-up status for Group 2 Elephants after Testing: Reformat – missing “g” at end of testing; all “p” s translating strange in other versions of Microsoft Word
Page 15, second paragraph: Several words have inappropriate spaces, e.g., “levofloxacin n”, “IN H”. This may be simply a problem with the draft version that is being circulated, but check master copy. Similar problem with “isoniazid” in third paragraph on page 16.
Page 19, last paragraph: Spacing problem again with “pyrazinamide” and “Il uroqoi nolones”
Page 23, Pharmacokinetics: Paragraph is represented as bolded in received draft version. Remove bolding.
Thank you for your thoughtful consideration of NASPHV review and input into the Guidelines. If you have any questions pertaining to our comments, please contact me by phone at 405.271.7637 or by email at Kristyb@health.ok.gov.

Sincerely,

Kristy Bradley, DVM, MPH, DACVP
Vice President, National Association of State Public Health Veterinarians
Office of the State Epidemiologist
Oklahoma State Department of Health
1000 NE Tenth Street, Room 606
Oklahoma City, OK 73117