Comparative Immunology, Microbiology and Infectious Diseases 36 (2013) 263–268

Contents lists available at SciVerse ScienceDirect

Comparative Immunology, Microbiology and Infectious Diseases

journal homepage: www.elsevier.com/locate/cimid

Review

One Health in the shrinking world: Experiences with tuberculosis at the human–livestock–wildlife interface

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ARTICLE INFO

Keywords:
Tuberculosis
One Health
Zoonoses
Human–animal interface
Mycobacterium tuberculosis
Mycobacterium bovis

ABSTRACT

Tuberculosis (TB) is a global anthropozoonotic infection that has raised awareness of the impact of disease at the human–livestock–wildlife interface. There are examples of transmission from livestock resulting in establishment of reservoirs in wildlife populations, and exposures from interactions between humans and wildlife that have resulted in disease outbreaks. A One Health approach is crucial to managing and protecting the health of humans, livestock, wildlife and the environment. Although still in its infancy in many areas of the world, the use of transdisciplinary teams to address wildlife–human–livestock boundary diseases will broaden the scope of options for solutions. This paper reviews some less commonly known examples of threats and outcomes using lessons learned from tuberculosis.

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1. Introduction

One Health embraces a holistic approach incorporating humans, animals, and the environment into a model where practitioners, scientists, stakeholders, and policymakers work toward the goal of ecosystem health [46]. Although tuberculosis (TB) is a regulated disease in most developed countries, it continues to be a global threat to the One Health paradigm. It serves as an example of the complexity of a disease that crosses boundaries between humans, livestock, and wildlife, and is impacted by the conditions of host, pathogen, environmental, political and socioeconomic factors. Studying tuberculosis in one set of hosts or environmental conditions may not be applicable to another. However using the principles of One Health, some

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0147-9571/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.cimid.2012.07.005

general lessons may be learned that may be useful to other disease scenarios.

Mycobacterial infections have existed from before recorded history [11]. *Mycobacterium tuberculosis* complex organisms have traditionally been associated with humans and domestic livestock. As molecular diagnostic and epidemiologic techniques have advanced, the detection of mycobacterial infection in new hosts has improved. No longer considered solely a disease of humans and livestock, tuberculosis has become established in wildlife populations [6] and threatens to spread as environmental, host, and pathogen characteristics change [22]. Specifically, the risk of *Mycobacterium bovis* infection at the "human–animal" interface has been recently reviewed by Michel et al. [35].

The tuberculous mycobacteria are considered significant global threats to human and animal health. The World Health Organization (WHO) estimates that one third of the world's human population is infected with tuberculosis [47]. WHO reported that in 2009 there were 9.4 million new TB human cases and approximately 1.7 million deaths attributed directly to TB (equal to 4700 deaths a day). *M. tuberculosis* is the etiologic agent of most human TB cases in the world. However, the number of cases of *M. bovis* in humans and animals is underestimated or unavailable in many areas of the world, especially in developing countries. *M. bovis* is still widespread in livestock in developing countries due to the lack of or sporadically applied control measures and pasteurization of milk and/or milk products [7]. The risk of disease transmission between species is increased when there is habitat encroachment by humans and livestock into wildlife areas, competition for resources between wildlife and livestock, and inadequate veterinary infrastructure for disease control. *M. bovis* has now become established in a number of wildlife reservoirs around the world due to the introduction and interaction with livestock [41].

A more holistic approach is required to address the public health, agricultural, conservation, management, and regulatory implications of this disease. An understanding of variations in pathogenesis and transmission is required for animal managers, regulatory decision-makers, clinicians, and scientists to create informed policies to protect human and animal health. Although tuberculosis classically presents as a pulmonary disease transmitted by aerosol, in some hosts, transmission routes may be through ingestion or bite wounds leading to infection of the gastrointestinal tract or skeletal system (for example, in carnivores) [34]. The One Health challenge is to develop new concepts about the pathogens, pathogenesis, comparative immunology of the various hosts, epidemiological dynamics and understand the role environmental factors play in each of the diverse systems. Lessons learned from the study of tuberculosis at interfaces may provide innovative approaches that may be applicable to other diseases affecting wildlife, livestock and humans. This paper reviews some less commonly known examples that illustrate the complexity of these interactions (Table 1) and the importance of One Health in addressing solutions to improve health.

Table 1
Examples of tuberculosis cases at human–livestock–wildlife interfaces.

Affected species	Suspected source	Country	Reference
Asian elephant	Humans	Nepal	[15]
Asian elephant	Humans	Thailand	[3]
Asian elephant	Humans	India	[15]
Chacma baboons	Humans	South Africa	[40]
Panther	Cattle	Argentina	[45]
American mink	Cattle	Argentina	[32]
Jaguar	Cattle	Venezuela/USA	[24]
Humans	Cattle products	USA	[42]
Humans	White rhinoceros	USA	[10]
Humans	Asian elephant	USA	[38]
Humans	Sea lions	Netherlands	[27]
African lions	African buffalo	South Africa	[41]
African buffalo	Cattle	South Africa	[41]
White-tailed deer	Cattle	USA	[6]
European badger	Cattle	UK/Ireland	[6]

2. Elephant–human interface in Asia

Habitat loss, human–elephant conflict, and disease are some of the factors that have contributed to the endangered status of the Asian elephant (*Elephas maximus*). One of the diseases that affects both ex situ and in situ captive elephants is tuberculosis caused by *M. tuberculosis*. It has been estimated that the prevalence could be as high as 11–25% in captive elephants (US, India, and Nepal) [15]. The Nepal Elephant HealthCare and TB Surveillance Program, a One Health Initiative, was created to integrate government, NGO, academic, human clinical and research resources to address TB as one of the cross-species issues in Nepal. During testing of the captive elephant population (85% completed), it was found that 23% of the elephants were serologically positive for tuberculosis. Nepal is considered to have a high rate of human tuberculosis (240/100,000) [43]. Therefore, it is hypothesized that due to the close contact between humans and working elephants, infected handlers may be serving as a source of infection for the animals. Similarly in Thailand, *M. tuberculosis* isolated from captive elephants was sequenced and strains appeared to have originated from humans [3].

From a conservation perspective, captive elephants play a critical role by patrolling national parks that provide habitat for other endangered species, create revenue through ecotourism, and convey educational messaging. An interface between the working and wild elephants occurs when individuals interact for breeding, or share feeding and watering areas. This raises the potential for direct transmission and environmental contamination with mycobacterial organisms from infected captive elephants as well as spillover to incidental hosts that also share these resources. The combination of high human disease prevalence, close human–captive elephant contact, and captive–wild elephant interface stress the importance of understanding the pathogenesis, epidemiology, and building the collaborative relationships that support the One Health approach to address the complexities of this issue.

Nepal's government has endorsed a nation-wide elephant TB testing program to identify and protect elephants and the public from further spread of the disease [15].

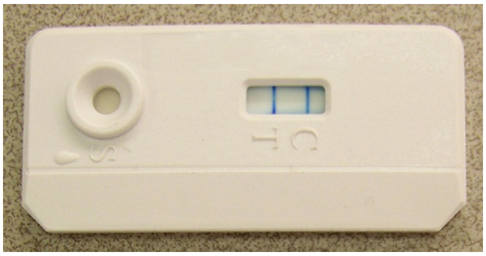

Fig. 1. Positive serological test from a *Mycobacterium tuberculosis*-infected elephant. Visual bands at T (test) and C (control) lines indicate that serum antibodies are present to mycobacterial antigens.

Infected elephants are quarantined and treated with anti-tuberculous drugs with the support of program partners. In addition, a human health monitoring program to screen elephant handlers has been instituted.

Research is underway to elucidate immune function in elephants to understand disease pathogenesis. Response to mycobacterial infection is dependent on both the humoral and cell-mediated immune responses. Elephants appear to develop a strong humoral response to *M. tuberculosis* infection (Fig. 1). This unique immunologic feature allows use of serological assays with high sensitivity and specificity for detection of infection in elephants since other diagnostic tests have relatively low sensitivity [31].

Altered immune function is considered one of the key factors affecting disease susceptibility to tuberculosis. The majority of species studied have shown an imbalance in T_H1–T_H2 cytokines. For example, most exposed humans develop an effective T_H1 immune response that prevents infection and progression to clinical disease [17]. Production of interferon (IFN-γ), tumor necrosis factor (TNF-α), interleukin-12 (IL-12), and interleukin-2 (IL-2) have been associated with effective T_H1 dominated immunity.

Preliminary comparison of mRNA levels for cytokines in *M. tuberculosis* complex seropositive and seronegative Asian elephants from Nepal showed that seropositive animals had higher levels of TNF-α, and lower levels of TGF-β than seronegative elephants [28]. Although not statistically significant, the seropositive elephants also had higher levels of IFN-γ and IL-4 with lower IL-10 and IL-12. These early investigations suggest that elephants may have a mixed T_H1–T_H2 response to *M. tuberculosis* infection, although more studies are needed.

By understanding factors that impact T cell function, such as stress, nutrition, co-infections, and environmental conditions, steps can be taken to minimize their effect and decrease the probability of acquiring an infection or shedding organisms if infected, thus breaking the cycle of transmission. However, key stakeholders and decision-makers must be educated to make informed choices in committing resources especially in developing countries as well as understanding how to protect public health, livestock, and wildlife populations.

3. Human–baboon interface in South Africa

Non-human primates are known to be susceptible to mycobacterial infections, usually acquired through contact with humans through captivity. However, environmental contamination may also be a source of infection for wild primates in contact with infected humans, their garbage, infected livestock or spillover species [14,26]. Researchers in South Africa tested fifty-one baboons using tuberculin skin tests and gamma interferon assays. Of the tested animals, two animals were confirmed to be infected with *M. tuberculosis* by positive gamma interferon tests antemortem and culture at necropsy [40].

On the Cape Peninsula in South Africa, twenty-seven free-living chacma baboons (*Papio ursimus*) were tested using the interferon gamma assay for tuberculosis, none of which tested positive [14]. As part of this study, it was concluded that baboons on the Cape Peninsula pose a low but potential risk for zoonoses transmission and that baboons might be at risk of being affected by anthroponoses. Chacma baboon troops frequently interact with tourists and raid local residential areas for food. This close contact increases the potential risk of direct and indirect transmission of zoonotic and anthroponotic diseases, which is a concern in South Africa due to the high prevalence of *M. tuberculosis* in the human population (768/100,000 during 2011) [9].

Conservation groups in South Africa have expressed concerns regarding baboon troops living at the Caledon's municipal dump site in which they reported that medical waste, animal carcasses and toxic pesticides have been illegally dumped creating an environmental scenario posing a health hazard to the baboons [18].

This complex interface illustrates the importance of a multidisciplinary approach to investigating and managing these types of interactions between baboons, humans and the environment. Estimating risk associated with cross-species disease transmission is very difficult and a challenge to stakeholders and policy-makers developing management plans. In addition, communities have cultural, economic, and social needs that must be taken into consideration in addressing health. Using the One Health approach to incorporate veterinarians, educators, epidemiologists, sociologists, public health professionals, engineers, physicians, economists, and other professionals has often been required to address political and social as well as scientific issues [33].

4. Human–mongoose interface in Botswana

An epizootic of tuberculosis occurred in Botswana in 1998–1999 affecting a troop of banded mongooses (*Mungos mungo*) [2]. A known human TB case was documented in the area of the mongoose study area. Infected animals were regularly observed feeding at the garbage pits associated with the human settlement. Lesions included enlarged cervical lymph nodes which ruptured and drained, creating a source of environmental contamination. From the initial case, all the troop members were affected and became emaciated with multifocal lymph node involvement, or disappeared. Although initial results concluded that the diagnosis was *M. tuberculosis*, later work confirmed that infection was caused by a novel member of the *M. tuberculosis* complex, *Mycobacterium mungi* [1]. This outbreak demonstrates the difficulty associated with investigating interface disease interactions. Many studies cannot perform speciation nor have the capacity to carry out molecular epidemiologic assessments.

The examples of outbreaks in the baboons and mongooses demonstrate the potential risks to wildlife in close association with humans, as well as confusion in assessing the hazards. A growing concern is the ecotourism industry and increased human–wildlife interface. As wildlife populations have greater and more diverse human contact, the risk of infectious disease may be more likely to emerge in either population. A better strategy to anticipate the exposure of wildlife and humans to disease transmission is required along with a broader understanding of the economic benefits of ecotourism balanced with the need for conservation.

5. Cattle–human–wildlife interface in Latin America

Comparatively less research has been done in Latin America compared to Africa on tuberculosis and wildlife–livestock–human interface, although faced with parallel problems of developing countries. Political instability, fragmented public health infrastructures, diversion of health resources, inadequate TB control programs, and continued relatively high rates of tuberculosis in certain Latin American countries play a role in the ongoing presence of tuberculosis [19]. Similar issues apply to TB programs for livestock [7].

Bovine tuberculosis is well-documented in cattle herds in many Latin American countries and presents the potential to spill over to humans or wildlife through unpasteurized milk, contaminated meat, or environmental contamination. In Brazil, *M. bovis* was isolated from 5.26% of milk samples from dairy cattle suspected of having tuberculosis but showing no clinical signs [39]. It is estimated that at least 47% of milk sold in Brazil was unpasteurized, presenting a significant risk of mycobacterial transmission. Shedding of mycobacteria from infected livestock creates an environmental hazard since studies have shown that *M. bovis* can persist up to 88 days in soil and 58 days in water [16].

Despite control measures, bovine TB is considered enzootic in Argentina and Venezuela, and sporadic in Brazil [7]. Environmental conditions, the potential interface with cattle, and routes of indirect transmission such as contaminated carcasses or pastures are important factors when considering the risk of infection to wildlife. There are only a few published studies that have surveyed free-ranging animals for tuberculosis in South America. Marsh deer (*Blastocerus dichotomus*) in Brazil were tested by collecting esophageal–pharyngeal fluids for DNA extraction and PCR using *M. tuberculosis* complex primers [30]. All 53 animals were negative, which was confirmed with necropsy and histopathology.

Unlike these more isolated ungulates, predators may be at greater risk. Infected cattle could present a threat to wild carnivores or scavengers through ingestion of infected meat or carrion or indirectly by eating insects that had contact with infected secretions. There has been one report of a wild panther with tuberculosis from Argentina although details are lacking [45]. Testing of an additional five panthers from the same area resulted in isolation of non-tuberculous mycobacterial species using bacteriological and molecular techniques.

In Argentina, the American mink (*Mustela vison*) was introduced to farms in the 1920s and subsequently escaped to form a free-ranging population. In the mid-2000s, during a logging operation near Buenos Aires, feral mink carcasses were found with lesions consistent with tuberculosis [32]. Based on histopathological examination and mycobacterial culture, a diagnosis of *M. bovis* was confirmed. Lesions were found in the digestive and respiratory tract. This is consistent with the natural route of infection in mink (oral). The discovery of TB in feral mink poses a potential threat to disease control if wild and domesticated animals share resources such as land or water. It also emphasizes the need for a One Health approach to determine environmental, livestock, and human interactions in this disease issue.

Due to the long incubation period of tuberculosis, there is the potential to move or translocate infection with the animal. A jaguar (*Panthera onca*) imported to a US zoo from Venezuela showed clinical signs consistent with tuberculosis and *M. bovis* was cultured on necropsy [24]. Serological testing of two other imported jaguars from Venezuela and three in Guyana were negative. However, the affected animal demonstrated reactivity to mycobacterial antigens MPB83 and 16/83 in serum collected prior to showing clinical signs of disease. This jaguar had arrived from an institution where whole carcass feeding was practiced and ingestion of infected meat was likely source of infection. For chronic infections such as tuberculosis, disease interface issues may cross international borders creating additional challenges.

Tuberculosis also may impact marine system health. Tuberculosis has been detected in wild South American fur seals (*Arctocephalus australis*), southern sea lions (*Otaria flavescens*), and fur seals (*Arctocephalus tropicalis*) along the coast of Argentina [4,5]. DNA fingerprints from the six fur seal stranding cases were similar to each other but differed slightly from the *M. bovis* found in humans and cattle in Argentina. Further studies have classified this as a novel organism, *Mycobacterium pinnipedii*, part of the *M. tuberculosis* complex, with seals as the natural hosts [8]. This organism can infect a variety of other species, with a potential for predators that feed on seals, as well as humans that handle infected animals.

6. Human–cattle interface: *M. bovis* and NTM infection in humans

The examples above have primarily focused on transmission of disease from humans and livestock into wildlife populations with potential of zoonotic infection. However, changes in the epidemiological landscape of the human–animal interface have resulted in greater awareness of the significance of bovine tuberculosis in human health, especially in developing countries. With few exceptions the literature indicates that *M. bovis* accounts for ~1% or less of TB cases in humans. For example, in the United States (US), in which differentiation between *Mycobacterium* spp. is routinely done among TB humans patients, results indicate that *M. tuberculosis* is responsible for approximately 98.6% of human infection and *M. bovis* only

1.4% [20]. However, the global picture of human TB caused by *M. bovis* is largely incomplete [44]. Even within the US, the risk of *M. bovis* infection differs among human populations. In San Diego, California 1994–2005, 45% of all TB cases in children and 6% of adults were caused by *M. bovis* [42].

Studies in different areas of the world reveal profound differences with regards to the proportion of human TB patients infected with *M. bovis* [21]. These are caused by different epidemiological environments associated with variable risks as well as the logistics and technical ability of laboratories to isolate and differentiate between *M. tuberculosis* complex species. A review of the risk of *M. bovis* infection at the "animal–human" interface, conducted by Michel et al. [35], found that infection in humans ranged from 0.5 to 30%.

Different sets of challenges and complexities are encountered by humans suffering from TB caused by *M. bovis* when compared to *M. tuberculosis*. *M. bovis* infection in humans is often associated with extra-pulmonary TB due to ingestion or handling of contaminated dairy products [7,12,13,25,29,42] which creates specific issues in terms of pathology and effective treatment compared to patients with pulmonary TB. In general, extra-pulmonary TB responds poorly to conventional anti-tuberculosis therapy. Studies reveal that treatment of *M. bovis* infected patients is longer [29] and has a higher mortality rate compared to *M. tuberculosis* infected patients [42]. This is usually due to the intrinsic resistance of *M. bovis* to pyrazinamide and may also by associated with multi-drug resistance [7].

It is also important to note the importance of non-tuberculous mycobacteria (NTM) infections in humans and animals in sub-Saharan Africa at the human–environment–livestock–wildlife interface. Synonyms for the NTM group of mycobacteria are atypical mycobacteria or mycobacteria other than tuberculosis (MOTT). Recent studies in pastoral ecosystems of Uganda detected NTM in humans with cervical lymphadenitis and cattle with lesions compatible with bovine tuberculosis [23].

7. Emerging concerns

With increasing numbers of captive wildlife in zoos, private sanctuaries, rehabilitation centers, and game parks, there is a greater potential for wildlife–wildlife and human–wildlife interactions. Although many institutions have veterinary programs that screen for tuberculosis in their collections, tuberculosis still exists in zoological collections worldwide [36]. In most situations, animal handlers and veterinary staff are considered to be at greatest risk of zoonotic disease transmission. This has been shown after caring for infected animals or attending a necropsy. At one zoo, seven of 24 zookeepers that had been exposed to an *M. bovis*-infected white rhinoceros (*Ceratotherium simum*) demonstrated conversion of their tuberculin skin test [10]. Cleaning of the barn was speculated to generate aerosols that results in infection of personnel. Similarly, employees that had skin conversions at another facility had been associated with training or attending the necropsy of two elephants (*E. maximus*) that were infected with *M. tuberculosis* [38]. Of interest, in addition to the two elephants, *M. tuberculosis* was also isolated from a black rhinoceros (*Diceros bicornis*) and two mountain goats (*Oreamnos americanus*). Although transmission between species was supported by molecular evidence, epidemiological investigations could not explain the route of transmission.

More recently, five staff members at an elephant sanctuary had tuberculin skin test conversions after being exposed by working in a barn with a *M. tuberculosis*-infected elephant [37]. This included elephant and administrative staff, suggesting aerosol transmission, since close contact was not required for conversion. Pressure washing was implicated in this outbreak.

Close contact can result in transmission between animals and to human handlers. An outbreak of tuberculosis in a sea lion colony, caused by *M. pinnipedii*, resulted in 13 out of 29 animals being positive [27]. Three of the animals had pulmonary involvement with one case being infectious. An investigation of the twenty-five animal handlers showed that six had positive skin tests and five were confirmed infected using the interferon gamma test. Aerosolization during cleaning was suspected as the route of transmission to the human cases.

8. Conclusion

Unique examples such as the human–captive elephant–wild elephant interface highlight the importance of an interdisciplinary approach that can influence large scale changes that impact health and conservation of an endangered species as well as human health. Outbreaks in sentinel populations at interfaces may reflect important changes in the environment or land use that increase risks for humans or animals (ex. TB in baboons). Inadequate TB control programs can have consequences for humans, livestock, and wildlife health, and lead to movement of disease with infected animals, animal products, or people. One Health implications of zoonotic diseases in animal venues where the public has potential contact with captive wildlife is a serious emerging concern, especially for immunocompromised individuals. Greater collaboration between public health officials, medical doctors, veterinarians, epidemiologists, scientists, animal managers, public stakeholders and policy-makers should be leveraged to address the concerns of interface diseases both in ex situ and in situ. A One Health approach is a better strategy to understand the complexities of mycobacterial infections at the interface of humans, livestock and wildlife in different environments worldwide.

References

[1] Alexander KA, Laver PN, Michel AL, Williams M, van Helden PD, Warren RM, et al. Novel *Mycobacterium tuberculosis* complex pathogen, *M. mungi*. Emerg Infect Dis 2010;16:1296–9.

[2] Alexander KA, Pleydell E, Williams MC, Lane EP, Nyange JFC, Michel AL. *Mycobacterium tuberculosis*: an emerging disease of free-ranging wildlife. Emerg Infect Dis 2002;8:598–601.

[3] Angkawanish T, Wajjwalku W, Sirimalaisuwan A, Mahasawangkul S, Kaewsakhorn T, Boonsri K, et al. *Mycobacterium tuberculosis*

infection of domesticated Asian elephants, Thailand. Emerg Infect Dis 2010;16:1949–51.
[4] Bastida R, Loureiro J, Quse V, Bernardelli A, Rodriguez D, Costa E. Tuberculosis in a wild subantartic fur seal from Argentina. J Wildl Dis 1999;35:796–8.
[5] Bernadelli A, Bastida R, Loureiro J, Michelis H, Romano MI, Cataldi A, et al. Tuberculosis in sea lions and fur seals from the south-western Atlantic coast. Rev Sci Tech Off Int Epi 1996;15:985–1005.
[6] Corner LAL. The role of wild animal populations in the epidemiology of tuberculosis in domestic animals: how to assess the risk. Vet Microbiol 2006;112:3003–312.
[7] Cosivi O, Grange JM, Daborn CJ, Raviglione MC, Fujikura T, Cousins D, et al. Zoonotic tuberculosis due to *Mycobacterium bovis* in developing countries. Emerg Infect Dis 1998;4:59–70.
[8] Cousins DV, Bastida R, Cataldi A, Quse V, Redrobe S, Dow S, et al. Tuberculosis in seals caused by a novel member of the *Mycobacterium tuberculosis* complex: *Mycobacterium pinnipedii* sp. nov. Int J Syst Evol Microbiol 2003;53:1305–14.
[9] Country South Africa stat (a) epidemiology and strategy, https://extranet.who.int/sree/Reports?op=Replet&name=%2FWHO_HQ_Reports%2FG2%2FPROD%2FEXT%2FTBCountryProfile&ISO2=ZA&outtype=html [accessed 30.01.12].
[10] Dalovisio JR, Stetter M, Mikota-Wells S. Rhinoceros' rhinorrhea: cause of an outbreak of infection due to airborne *Mycobacterium bovis* in zookeepers. Clin Infect Dis 1992;15:598–600.
[11] Daniel TM. The history of tuberculosis. Respir Med 2006;100: 1862–70.
[12] Danker WM, Davis CE. *Mycobacterium bovis* as a significant cause of tuberculosis in children residing along the United States–Mexico border in the Baja California region. Pediatrics 2000;105: E79.
[13] de Kantor IN, LoBue PA, Thoen CO. Human tuberculosis caused by *Mycobacterium bovis* in the United States, Latin America, and the Carribean. Int J Tuberc Lung Dis 2010;14:1369–73.
[14] Drewe JA, O'Riain MJ, Beamish E, Currie H, Parsons S. Survey of infections transmissible between baboons and humans, Cape Town, South Africa. Emerg Infect Dis 2012;18:298–301.
[15] Elephant TB Initiative – Nepal TB Project, http://www.elephantcare.org/tbnepal.htm [accessed 27.01.12].
[16] Fine AE, Bolin CA, Gardiner JC, Kaneene JB. A study of the persistence of *Mycobacterium bovis* in the environment under natural weather conditions in Michigan, USA. Vet Med Int 2011:12 p, http://dx.doi.org/10.4061/2011/765430. Article ID 765430.
[17] Flynn JL, Chan J. Immunology of tuberculosis. Ann Rev Immunol 2001;19:92–129.
[18] Gosling M. Baboons get TB as medical waste is dumped. February 19, 2004. www.iol.co.za [accessed 31.01.12].
[19] Granado M. Tuberculosis profile in Latin America; impact of political turmoil on TB control, http://www.bc.lung.ca/association_and_services/uiatld-pdfs/Profile%20of%20TB%20in%20Latin%20America%20-%20Dr.pdf; 2007 [accessed 30.01.12].
[20] Hlavsa M, Moonan P, Cowan L, Navin T, Kammerer S, Morlock G, et al. Human tuberculosis due to *Mycobacterium bovis* in the United States, 1995–2005. Clin Infect Dis 2008;47:168–75.
[21] Huchzermeyer HFAK, de Kantor I, Merslin FX. Zoonotic tuberculosis due to *Mycobacterium bovis* in developing countries. Emerg Infect Dis 1998;4:59–70.
[22] Humblet MF, Boschiroli ML, Saegerman C. Classification of worldwide bovine tuberculosis risk factors in cattle: a stratified approach. Vet Res 2009;40:50–73.
[23] Kankya C, Muwonge C, Djønne B, Munyeme M, Opuda-Asibo J, Skjerve E, et al. Isolation of non-tuberculous mycobacteria from pastoral ecosystems of Uganda: public health significance. BMC Public Health 2011;11:320.
[24] Kapustin N, Ball R, Teare JA, Greenwald R, Esfandiari J, Lyashchenko K. Tuberculosis diagnosis in jaguar (*Panthera onca onca*) and addra gazelle (*Gazella dama rugicollis*) using multiple antigen print immunoassay and rapid lateral flow technology. Proc Am Assoc Zoo Vet 2006:257–60.
[25] Kazwala RR, Daborn CJ, Sharp JM, Kambarage DM, Jiwa SF, Mbem-bati NA. Isolation of *Mycobacterium bovis* from human cases of cervical adenitis in Tanzania: a cause for concern. Int J Tuberc Lung Dis 2001;5:87–91.
[26] Keet DF, Kriek NP, Bengis RG, Grobler DF, Michel A. The rise and fall of tuberculosis in a free-ranging chacma baboon troop in the Kruger National Park. Ondest J Vet Res 2000;67: 115–22.
[27] Kiers A, Klarenbeek A, Mendelts B, Van Soolingen D, Koeter G. Transmission of *Mycobacterium pinnipedii* to human in a zoo with marine mammals. Int J Tuberc Lung Dis 2008;12: 1469–73.
[28] Landolfi JA, Mikota SK, Chosy J, Lyashchenko KP, Giri K, Gairhe K, et al. Comparison of systemic cytokine levels in *Mycobacterium* spp. seropositive and seronegative Asian elephants (*Elephas maximus*). J Zoo Wildl Med 2010;41:445–55.
[29] LoBue PA, Moser KS. Treatment of *Mycobacterium bovis* infected tuberculosis patients: San Diego County, California, United States, 1994–2003. Int J Tuberc Lung Dis 2005;9:333–8.
[30] Luna JO, Santos MAA, Durigon EL, Araujo JP, Duarte JMB. Tuberculosis survey of free-ranging marsh deer (*Blastocerus dichotomus*) in Brazil. J Zoo Wildl Med 2002;34:414–5.
[31] Lyashchenko KP, Greenwald R, Esfandiari J, Olsen JH, Ball R, Dumonceaux G, et al. Tuberculosis in elephants: antibody responses to defined antigens of *Mycobacterium tuberculosis*, potential for early diagnosis, and monitoring of treatment. Clin Vacc Immunol 2006;13:722–32.
[32] Martino P, Gatti M, Bautista E, Stanchi N. Case report: tuberculosis in introduced American mink Mustela vison, http://smallcarnivoreconservation.org/sccwiki/images/c/cc/SCC36_Martino_et_al.pdf; 2007 [accessed 31.01.12].
[33] Mazet JAK, Cliffort DL, Coppolillo PB, Deolalikar AB, Erickson JD, Kazwala RR. A One Health approach to address emerging zoonses: the HALI project in Tanzania. PLoS Med 2009;6:1–6.
[34] Michel A, Bengis RG, Keet DF, Hofmeyr M, de Klerk LM, Cross PC, et al. Wildlife tuberculosis in South African conservation areas: implications and challenges. Vet Microbiol 2006;112:91–100.
[35] Michel A, Müller B, van Helden P. *Mycobacterium bovis* at the animal–human interface: a problem, or not. Vet Microbiol 2010;140:371–81.
[36] Montali RJ, Mikota SK, Cheng LI. *Mycobacterium tuberculosis* in zoo and wildlife species. Rev Sci Tech Off Int Epiz 2001;20:291–303.
[37] Murphree R, Warkentin JV, Dunn JR, Schaffner W, Jones TF. Elephant-to-human transmission of tuberculosis, 2009. Emerg Infect Dis 2011;17:366–71.
[38] Oh P, Granich R, Scott J, Sun B, Joseph M, Stringfied C, et al. Human exposure following *Mycobacterium tuberculosis* infection of multiple animal species in a metropolitan zoo. Emerg Infect Dis 2002;8:1290–3.
[39] Pardo RB, Langoni H, Mendonca LJP, Chi KD. Isolation of *Mycobacterium* spp. In milk from cows suspected or positive to tuberculosis. Braz J Vet Res Anim Sci 2001;38:284–7.
[40] Parsons SDC, Gous TA, Warren RM, de Villiers C, Seier JV, van Helden PD. Detection of *Mycobacterium tuberculosis* infection in chacma baboons (*Papio ursinus*) using the QuantiFERON-TB Gold (In-Tube) assay. J Med Primatol 2009;38:411–7.
[41] Renwick AR, White PCL, Bengis RG. Bovine tuberculosis in southern African wildlife: a multi-species host–pathogen system. Epidemiol Infect 2007;135:529–40.
[42] Rodwell TC, Moore M, Moser KS, Brodine SK, Strathdee SA. *Mycobacterium bovis* tuberculosis in binational communities. Emerg Infect Dis 2008;14:1–16.
[43] TB in South-East Asia – Country Profiles – Nepal, http://www.searo.who.int/en/Section10/Section2097/Section2100_14801.htm [accessed 30.01.12].
[44] Thoen C, LoBue P, de Kantor I. Why has zoonotic tuberculosis not received much attention? Int J Tuberc Lung Dis 2010;14:1073–4.
[45] Traversa MJ, Etchechoury I, Jorge MC, Schettino DM, Bernadelli A, Zumarraga M, et al. Mycobacterial isolation from *Felis concolor* in captivity. Braz J Vet Res Anim Sci 2009;46:25–31.
[46] United Nations Contributing to One World, One Health: a strategic framework for reducing risk of infectious diseases at the animal–human–ecosystem interface. FAO/OIE/WHO/UNICEF/UNSIC/World Bank, http://un-influenza.org/files/OWOH_14Oct08.pdf; 2008 [accessed 30.01.12].
[47] World Health Organization Tuberculosis, http://www.who.int/mediacentre/factsheets/fs104/en; 2012 [accessed 03.02.12].