The Risk of Tuberculosis Transmission to Free-Ranging Great Apes

TIFFANY M. WOLF1,2*, SRINAND SREEVATSAN3, DOMINIC TRAVIS3, LAWRENCE MUGISHA4,5, AND RANDALL S. SINGER1

1Department of Veterinary and Biomedical Sciences, College of Veterinary Medicine, University of Minnesota, St. Paul, Minnesota
2Minnesota Zoological Gardens, Apple Valley, Minnesota
3Department of Veterinary Population Medicine, College of Veterinary Medicine, University of Minnesota, St. Paul, Minnesota
4College of Veterinary Medicine, Animal Resources and Biosecurity, Makerere University, Kampala, Uganda
5Conservation and Ecosystem Health Alliance (CEHA), Kampala, Uganda

Pathogen exchange between humans and primates has been facilitated by anthropogenic disturbances, such as changing land use patterns, habitat destruction, and poaching, which decrease population sizes and increase levels of primate–human interaction. As a result, human and domestic animal diseases have become a recognized threat to endangered primate populations. Tuberculosis is a major global human and animal health concern, especially in equatorial Africa where many of the remaining free-living great ape populations exist in proximity with exposed and/or infected human populations and their domestic animals. Increased anthropogenic pressure creates an opportunity for the anthropozoonotic spread of this disease. This review examines current evidence of the risk of tuberculosis transmission to great apes, the benefits and limitations of current detection methods, the impact of current great ape conservation and management strategies on this risk, and the need for an ecosystem health-based approach to mitigating the risks of tuberculosis transmission to great apes. Am. J. Primatol. 76:2–13, 2014. © 2013 Wiley Periodicals, Inc.

Key words: great apes; tuberculosis; anthropozoonotic disease transmission

INTRODUCTION

In 2011, there were an estimated 8.7 million new cases of tuberculosis among humans worldwide, with a global prevalence of approximately 170 cases per 100,000 people [WHO, 2012]. This global pandemic is primarily caused by Mycobacterium tuberculosis, of which humans are the natural host, although other pathogenic mycobacteria of the M. tuberculosis Complex (MTC), such as Mycobacterium africanum and Mycobacterium bovis, also play a role in human infection [Cosivi et al., 1999; Gagneux, 2012; Kazwala et al., 2001]. Tuberculosis is predominantly a pulmonary disease, spread when bacteria are expelled from the lungs with the onset of active disease, but it may also present as extra-pulmonary disease involving other organs of the body [WHO, 2012]. Among humans infected with M. tuberculosis, only about 5–10% develop active disease and become infectious, while the remainder either eliminate infection or remain latently infected and do not transmit infection [Gagneux, 2012; Palomino et al., 2007; WHO, 2012]. However, those co-infected with human immunodeficiency virus (HIV) are much more likely to develop active disease [Cosma et al., 2003; Gagneux, 2012; Palomino et al., 2007; WHO, 2012]. Advances in molecular research are revealing much more genomic heterogeneity of M. tuberculosis strains than previously recognized [Cosma et al., 2003; Gagneux, 2012; Hershberg et al., 2008; Sreevatsan et al., 1997]. This genomic diversity has been linked to function and may explain some of the observed differences in infection outcome, disease progression, and transmission among infected humans [De Jong et al., 2008; Gagneux, 2012; Hershberg et al., 2008; Portevin et al., 2011].

Contract grant sponsor: Zoetis/Morris Animal Foundation Veterinary Research Fellowship; contract grant sponsor: Consortium on Law and Values in Health, Environment & the Life Sciences of the University of Minnesota; contract grant sponsor: Minnesota Zoo; contract grant sponsor: USDA-NIFA Specials Grant on Bovine Tuberculosis; contract grant sponsor: Veterinary Population Medicine Department of the University of Minnesota’s College of Veterinary Medicine

Conflicts of interest: None

*Correspondence to: Tiffany M. Wolf, 205 Veterinary Sciences Building, University of Minnesota, 1971 Commonwealth Avenue, St. Paul, MN 55108. E-mail: wolfx305@umn.edu

Received 8 December 2012; revised 25 July 2013; revision accepted 29 July 2013

DOI: 10.1002/ajp.22197
Published online 5 September 2013 in Wiley Online Library (wileyonlinelibrary.com).

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Until recently, infection with *M. tuberculosis* or any other MTC member has never been detected in free-ranging great ape populations, and many argue that contact between great apes and *M. tuberculosis* infected humans is insufficient for transmission to susceptible free-ranging great apes. However, as tuberculosis remains a major global human health threat and contact rates between humans and great apes increase with habitat encroachment, forest fragmentation, and conservation-driven research and ecotourism, the risk of tuberculosis transmission from humans to great apes must be continuously assessed. Moreover, transmission pathways from humans through other animal hosts whose contact with humans and great apes are high must be closely evaluated. Spillover of MTC infection from domestic animals and possibly humans into free-living monkey populations is well documented and may be an important source of transmission of human or domestic animal tuberculosis infection to great apes [Keet et al., 2000; Sapolsky & Else, 1987; Tarara et al., 1985; Wilbur et al., 2012]. A recent diagnosis of tuberculosis infection in a wild chimpanzee by a novel MTC strain underscores the knowledge gaps on the epidemiology and impact of tuberculosis to primate conservation [Coscolla et al., 2013]. The existence of great ape species in small, isolated populations requires that the long-term impact of tuberculosis transmission on population persistence be considered when characterizing this risk of disease caused by members of the MTC. Here we review reports on disease transmission, great ape conservation strategies, tuberculosis infection in non-human primates, and current methods of detection to demonstrate that tuberculosis transmission is a realistic threat for great ape conservation. Further, we identify specific areas where more research is needed to fully characterize this disease threat for great ape populations and demonstrate the need for an ecosystem health-based approach to mitigate this transmission risk. This review focuses on African populations of great apes, although many of the arguments presented here have application in Asian populations as well.

**DISCUSSION**

**Disease Transmission Between Humans and Great Apes**

Most extant great ape populations exist in fragmented populations distributed across equatorial Africa. These populations include Eastern (Gorilla beringei) and Lowland (Gorilla gorilla) gorillas, bonobos or pygmy chimpanzees (Pan paniscus), and common chimpanzees (Pan troglodytes) [Fruth et al., 2008; Oates et al., 2008; Robbins & Williamson, 2008; Walsh et al., 2008]. Eastern gorillas, of which there are two subspecies, mountain gorillas (G. b. beringei) and Eastern lowland gorillas (G. b. graueri) can be found in Uganda, Rwanda, and the Democratic Republic of Congo (DRC) [Robbins & Williamson, 2008]. Lowland gorilla (G. gorilla) populations, also consisting of four subspecies (G. g. gorilla and G. g. diehli), exist in forest fragments of several western African countries, such as Angola, Nigeria, Cameroon, Congo, and Gabon [Walsh et al., 2008]. While bonobo populations are limited to DRC, common chimpanzee populations, consisting of four subspecies (Pan troglodytes verus, P. t. ellioti, P. t. troglodytes, and P. t. schweinfurthii), are the most widely distributed of the great apes, stretching discontinuously across equatorial Africa from southern Senegal to western Tanzania and Uganda [Fruth et al., 2008; Oates et al., 2008]. All of these great ape populations are declining and are currently listed by the International Union for Conservation of Nature as endangered or critically endangered [Fruth et al., 2008; Oates et al., 2008; Robbins & Williamson, 2008; Walsh et al., 2008]. Each of these species are threatened by infectious diseases such as Ebola and a range of human pathogens, although differences in species behavior and social organization may be influencing exposure to and population impacts associated with certain pathogens [Nunn et al., 2003, 2007].

There is accumulating evidence indicating that great apes are exposed to and, in some cases, suffer disease from human and domestic animal pathogens [Kaur et al., 2008; Køndgen et al., 2008; Palacios et al., 2011; Rwego et al., 2008; Whittier, 2009; Williams et al., 2008]. There have been numerous independent reports of disease outbreaks among great ape populations across Africa in which pathogens have been linked to transmission from humans (Table I). In many of these epidemics, a definitive diagnosis of the etiological agent was not conclusively determined. In these cases, transmission from humans is speculative, based on circumstantial evidence associating animal behavior, clinical disease signs, and contact with local infected humans. However, in recent years molecular epidemiological methods have significantly improved our abilities to more definitively determine the role of human pathogen transmission in the occurrence of infectious disease outbreaks among great apes. For example, several outbreaks of respiratory disease in chimpanzees of Taï National Forest, Côte d’Ivoire were determined by molecular techniques to be caused by human metapneumovirus (HMPV) and respiratory syncytial virus (HRSV) [Køndgen et al., 2008, 2010]. Gene sequencing and phylogenetic analyses of HMPV and HRSV PCR products revealed virus strains to be closely related to those circulating in the human population, providing the first evidence for human disease transmission into a great ape population. Subsequently, HMPV infection has also
<table>
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<th>Location</th>
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<td>Respiratory disease</td>
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<td>Chimpanzees</td>
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<td>Respiratory disease</td>
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<td>92/2</td>
<td>Human metapneumovirus</td>
<td>Palacios et al. [2011]</td>
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<sup>a</sup>Morbidity is represented as the percentage of the total population that demonstrated clinical signs of disease, whereas mortality is the total number of deaths associated with the epidemic.  
<sup>b</sup>There is strong molecular evidence that the etiological agents associated with these outbreaks originated from humans.
been associated with separate respiratory outbreaks among chimpanzees of Mahale Mountains National Park, Tanzania and mountain gorillas of Virunga Massif, Rwanda using PCR and phylogenetic analyses [Kaur et al., 2008; Palacios et al., 2011]. These findings demonstrate that sufficient contact between humans and great apes exists which enables the transmission of certain human pathogens, but much remains to be learned about such contact, the dynamics of these transmission events, and if these coupling points between humans and great apes would facilitate the transmission of other human pathogens.

Microbial transmission from humans to free-living great apes and other primates has also been documented beyond the scope of outbreak investigation. Several studies of antimicrobial resistance and genetic relatedness of enteric bacteria have shown that bacterial isolates from primates living in close proximity to humans share similar antimicrobial resistance patterns and are more genetically related to isolates from humans, as opposed to isolates from primates not living in close proximity to humans [Goldberg et al., 2008; Rwego et al., 2008]. These studies highlight the significance of environmental transmission of microorganisms and potential pathogens between humans and great apes.

Besides patterns of contact arising from anthropogenic impacts on the natural environment (e.g., habitat fragmentation and increased human densities surrounding great ape habitat), pathogen transmission has been associated with human habitation of great apes for research and ecotourism [Homsy, 1999; Kondgen et al., 2008]. Human habitation, a tool utilized in the conservation of endangered great apes, entails the conditioning of these animals to close encounters with human observers. The benefits of human habitation to great ape survival have been realized through the reduction of poaching and habitat loss in areas where research and ecotourism exist [Campbell et al., 2011; Kondgen et al., 2008; Pusey et al., 2007]. Thus, to maintain the benefits of habitation and mitigate the disease risks, managers must consider the health of the humans in contact with these animals: tourists, researchers, park workers, and local humans living in proximity or within the parks.

Tourists have been a primary focus in assessing disease risks to great apes given their potential for introducing new pathogens into an ecosystem [Homsy, 1999; Sandbrook & Semple, 2007; Woodford et al., 2002]. It has been shown that human behaviors, such as defecating, urinating, poor waste disposal, and aerosol contamination through sneezing and coughing, within and in proximity to mountain gorilla habitat are a health risk to mountain gorilla populations, with local communities posing the greatest risk [Nizeyi et al., 2012]. Thus, as we consider endemic disease risks to habituated great apes, it becomes clear that contact between great apes and local humans may pose a risk for the transmission of M. tuberculosis and other pathogenic members of the MTC, pathogens which may have a high prevalence in local African human and domestic animal populations and which may have potentially devastating effects on great ape populations.

The Risk of Tuberculosis Transmission to Great Apes

With an initial assessment of the risk of tuberculosis transmission from humans to great apes, it may be hypothesized that the risk is fundamentally related to the incidence of active infection in the local human or animal populations with which great apes have contact. In the most basic Susceptible-Infectious-Recovered (SIR) transmission models, contact rate and increasing incidence of infectiousness drive transmission. Thus, in areas where human or domestic animal tuberculosis is higher and there is contact with great apes or other primates, higher transmission risk would be expected. Conversely, in areas where human/domestic animal tuberculosis and/or great ape contact is lower, the risk would inherently be lower. According to the 2012 WHO Global Tuberculosis Control report, among the 8.7 million global incident cases of human tuberculosis, 24% of these occurred in Africa [WHO, 2012]. Furthermore, the geographical distribution of African great ape habitat falls within countries that have some of the world’s highest rates of human tuberculosis, ranging from 50 to over 300 incident cases per 100,000 people (Fig. 1) [WHO, 2012]. These statistics as well as the high prevalence of HIV co-infection among humans in this region raises additional concern for transmission risk, as co-infection with HIV generally results in a higher likelihood of active tuberculosis. Furthermore, recent evidence of MTC DNA among populations of free-ranging synanthropic macaques demonstrates that frequent human contact and high tuberculosis prevalence within the human population increases the risk of tuberculosis for non-human primate populations [Wilbur et al., 2012]. Unfortunately, the epidemiology of tuberculosis is not so simple as to be explained by basic SIR models. For instance, most human infections are latent and therefore not infectious, which complicates assessments of risk. Additionally, the contact needed for tuberculosis...
transmission among humans is typically close and sustained, which is generally not characteristic of the contact between humans and free-living great apes. Thus, increases in human tuberculosis incidence will not necessarily be linearly related to the tuberculosis risk for great apes, particularly if other hosts are involved in transmission of infection. Moreover, much remains to be understood about the observed variation in susceptibility and transmission of different M. tuberculosis strains among humans and the genetic drivers of these events before reasonable predictions can be made about risk to primates [Gagneux, 2012]. However, as basic science and epidemiological research enhances our understanding of this variability among humans, our ability to predict this risk for primate populations will also advance.

A survey conducted in 2000 of local inhabitants of Bwindi Impenetrable Forest National Park, Uganda found that despite a high level of respiratory symptoms in the region, many people were not tested for tuberculosis and infection status was largely unknown [Guerrera et al., 2003]. These data suggest that many cases of tuberculosis may go undetected and untreated. This situation is slowly changing as global efforts and funding for tuberculosis control are increasing, especially in areas of Africa with high HIV prevalence [WHO, 2012]. Since park workers
employed to protect great apes originate from these local communities, updated information on the tuberculosis status and awareness among these communities would be valuable to both public health and great ape conservation. While population managers generally recognize concern for tuberculosis introduction and guidelines for tuberculosis testing among park employees have been developed, employee health and disease screening programs have not yet been widely adopted for park workers [Ali et al., 2004; WCS, 2005].

Many parks have established rules to reduce pathogen transmission from humans to great apes, such as restricting great ape visitation by people who are ill and coughing, or through vaccination [Homsy, 1999; Williamson & Macfie, 2010]. As M. tuberculosis is generally transmitted by the aerosolization of infectious particles (through coughing, talking, or sneezing) that can be suspended in the air for hours before being inhaled, such park rules should prevent the transmission of this pathogen to great apes from infectious people with pulmonary tuberculosis simply by eliminating contact [Baker, 1995]. Although this rule may not capture people infected with gastrointestinal tuberculosis, who may be shedding high numbers of organism in their stool, other rules restricting defecation within great ape habitat should reduce such a risk [Rasheed et al., 2007; Sharma & Bhatia, 2004]. However, as habitat use by non-research and non-tourist humans increases, the risks of disease transmission that are mitigated by these rules might be expected to increase. Additionally, in situations where park workers, researchers, or other local humans reside within the park and great apes enter areas of human habitation, restricting visitation by ill humans may not be enough to completely eliminate contact and transmission that may occur within these areas of human habitation. Furthermore, the use of vaccination in humans as a preventative measure may provide a false sense of security; as bacille Calmette-Guérin (BCG), the only vaccine available against tuberculosis, does not reliably protect against pulmonary tuberculosis [Russell et al., 2010].

Indirect routes of transmission such as contamination and pathogen persistence in the environment should also be considered as possible pathways for tuberculosis transmission. Great apes that frequent areas of human habitation, either within or outside of parks, may be at greatest risk for both direct and indirect transmission. For example, M. tuberculosis (as well as other respiratory pathogens) may be transmitted via interaction with contaminated objects (i.e., fomites)—such as tissues or handkerchiefs—that capture the attention of curious great apes, which often touch, smell, and potentially consume such novel objects [Wallis & Lee, 1999; Woodford et al., 2002]. In general, Mycobacterium species are well adapted to survival in harsh environments, with the lipid-rich, protective cell wall, slow growth rate, and long dormancy [Baker, 1995; Chadwick, 1981; Palomino et al., 2007]. Environmental contamination and fomites have been implicated in the transmission of MTC organisms (e.g., M. bovis, M. mungi) between wildlife, humans, and domestic animals [Alexander et al., 2010; Courtenay et al., 2006; Tarara et al., 1985]. Further, other primate or wildlife species may serve as a vector for transmission of tuberculosis (human, bovine or other) into great ape populations. The role of environmental, fomite, or vector species transmission in other human respiratory pathogen outbreaks among great apes has not yet been assessed, but should be explored when weighing the risks of tuberculosis transmission into great ape and other primate populations.

Another potential source of human tuberculosis for free-living great ape populations is the reintroduction of rehabilitated great apes by primate sanctuaries. Great apes at these facilities originate from diverse locations throughout Africa in various states of health and have assorted histories of human contact [Mugisha et al., 2011; Schoene & Brend, 2002]. These sanctuaries are challenged with managing injuries and illnesses in the face of limited resources. Crowded conditions and animal stress contribute to efficient disease transmission, and cross-species transmission between animals and human caretakers is a significant concern. This concern was exemplified in a recent study of Staphylococcus aureus epidemiology in African sanctuaries where chimpanzees were found infected with a variety of human-associated, multi-drug resistant strains of S. aureus, indicating transmission from their human caretakers [Schaumburg et al., 2012b]. Tuberculosis outbreaks have also been diagnosed within primate sanctuaries and are particularly concerning given the challenges of early detection, diagnosis, and management of infected individuals with limited resources [Unwin et al., 2012]. The number of great apes turned over to sanctuaries for medical care and rehabilitation is increasing, and interest in reintroduction of these animals into their natural habitat. Given the current challenges of disease screening in these settings, rehabilitated animals would pose a significant risk for the introduction of tuberculosis and other human pathogens into presumably naive free-living populations.

Understanding pathogen transmission across host species within an ecosystem is a complex task, particularly when several closely related pathogens are circulating and causing disease. This is certainly an issue in human medicine, where closely related members of the Mycobacterium genus have been responsible for disease in humans. For example, M. bovis, the etiologic agent of bovine tuberculosis and close relative of M. tuberculosis in the MTC, has been documented in cases of extrapulmonary tuberculosis in rural Tanzania [Kazwala et al., 2001, 2006].
Unfortunately, it is not easily distinguished from *M. tuberculosis* when culture is unavailable, thus its contribution to the tuberculosis epidemic in humans is not fully understood [Cleaveland et al., 2007; Kazwala et al., 2001]. Moreover, despite a growing body of evidence for the zoonotic potential of *M. bovis*, developing countries often lack regulations for control and prevention of infection in livestock, and general knowledge regarding risks of infection are lacking [Cosivi et al., 1999; Michel et al., 2010].

The distinction between *Mycobacterium* species is relevant with regard to the source of transmission and how these pathogens are transmitted between species. Although humans may be infected with and suffer disease from either *M. tuberculosis* or *M. bovis*, a much higher prevalence of *M. tuberculosis* has been documented in humans with tuberculosis [Kazwala et al., 2001, 2006]. Additionally, the transmission of *M. tuberculosis* among humans (e.g., via aerosolized infectious organisms) is generally different than the transmission of *M. bovis* to humans (e.g., via unpasteurized milk and exposure to infected animal tissues) [Baker, 1985; Cosivi et al., 1999]. On the contrary, livestock with tuberculosis are typically infected with *M. bovis* and not *M. tuberculosis*, and are generally infected by *M. bovis* through aerosolized infectious organisms from conspecifics or through exposure to infectious materials such as feces and urine from alternative hosts sharing their environment (as observed with wildlife hosts such as badgers in Britain) [Courtenay et al., 2006; Morris et al., 1994]. This distinction between *Mycobacterium* species becomes important when discussing transmission risk as these organisms are transmitted between species and through the environment by different mechanisms and pathways, which in turn impacts the risk of exposure to these pathogens for primates within their own environment. Therefore, to further consider strategies that might reduce the risk of disease in primate populations, it is important to evaluate *Mycobacterium* species-specific differences (including infected source populations) in transmission that might impact primate exposure.

Given the phylogenetic similarity of humans and great apes, as well as evidence of *M. bovis* infection in free-living baboon populations, it may be presumed that great apes share a similar risk of infection by *M. bovis* [Keet et al., 2000; Sapolsky & Else, 1987; Tarara et al., 1985]. Species such as baboons, whose behavior brings them in frequent contact with humans, livestock, and great apes, might be potential coupling points for disease transmission across some of these populations that might not otherwise come into direct contact [Keet et al., 2000; Müller-Graf et al., 1997; Murray et al., 2000]. Thus, to fully understand the risk of tuberculosis transmission to great apes, the prevalence of *M. bovis* in local livestock as well other wildlife species (e.g., baboons or other monkeys) must also be considered.

**Tuberculosis Infection in Primates**

Much of our understanding of naturally acquired tuberculosis infection in great apes and monkeys originates from observations of captive animals [Diniz et al., 1983; Loomis, 2003; Michel et al., 2003; Michel & Huchzermeyer, 1998]. Clinical signs are absent in latent infection, but quite varied with active disease, ranging from nonspecific abnormalities, such as anorexia, lethargy, or weight loss to respiratory signs such as tachypnea or coughing [Diniz et al., 1983; Michel et al., 2003]. Extrapulmonary infection results in changes in health associated with the tissue of infection (e.g., draining abscessation, hemorrhagic diarrhea) [Michel et al., 2003]. Pathologic lesions may be characterized by infiltrates or cavitations of the lungs or other infected tissues, including lymph nodes, bone, kidney, central nervous system, and others. Within the realm of captive management, there is much concern for the transmission of tuberculosis from humans to great apes, due to the recognized susceptibility of great apes to tuberculosis [Loomis, 2003; Michel & Huchzermeyer, 1998]. It is difficult, however, to predict how susceptibility, disease, and transmission of tuberculosis as observed among captive great apes might translate to free-ranging populations. Certainly stress, social interactions, human contact, and activity patterns can strongly influence susceptibility and disease; however, the difficulties in measuring these factors for direct comparison of captive and free-ranging populations challenges our ability to extrapolate from our knowledge of this disease in captivity to estimate the risk of infection and potential impacts on free-ranging populations.

A recent diagnosis of MTC infection in a wild chimpanzee is our first glimpse of tuberculosis infection in free-ranging great apes [Coscolla et al., 2013]. In this report, researchers describe the identification of a genetically distinct MTC strain of tuberculosis, most closely related to Lineage 6 (i.e., *M. africanum* West-Africa type-2), on a routine necropsy of an aged female chimpanzee killed by a leopard in Tai National Forest. Aside from deteriorating body condition over a period of years, the report indicated no other clinical signs associated with the extra-pulmonary tuberculosis infection. The investigators further report that despite extensive necropsies and molecular screens of other chimpanzees in the region, this appears to be a unique finding, and it is yet unknown as to whether this novel strain is a chimpanzee-specific pathogen or one transmitted from another primate or animal host. Although most closely related to human-associated strains of tuberculosis, the results of this investigation do not suggest that infection originated from humans. Undoubtedly, this finding warrants more active investigations into the prevalence of this pathogen and the genetic diversity of tuberculosis infection among free-living.
primates to better understand the epidemiology and impact of tuberculosis infection to the conservation of these populations.

There are inherent challenges in positively identifying tuberculosis in great apes. Multiple diagnostic modalities, typically relying on the demonstration of tissue lesions, host immune responses, or culture of the organism, are required for the diagnosis in great apes by standard methods [Lin et al., 2008; Miller, 2008]. Reliance on these traditional tuberculosis test methods makes tuberculosis surveillance impractical given the need for animal handling and anesthesia for collection of the necessary diagnostic specimens. Thus, the detection of tuberculosis in free-ranging species has been mostly limited to post-mortem diagnosis, at which time transmission of tuberculosis may be well advanced through a social primate group. Given these limitations, without systematic monitoring of population health accompanied by recovery and post-mortem examination of all carcasses, a low level of tuberculosis infection among a great ape population might go undetected. To overcome this potential problem, consideration must be given to the application of molecular methods of pathogenic organism detection in the development of non-invasive methods of tuberculosis diagnosis.

Non-invasive sampling refers to the collection of biological samples without the need for animal handling or anesthesia. Such methods have been useful in the screening of saliva, feces and urine for systemic, gastrointestinal, and respiratory pathogens of great ape populations [Gillespie et al., 2010; Kaur et al., 2008; Keele et al., 2009; Kõndgen et al., 2010; Liu et al., 2008; Makuwa & Souquiere, 2003; Rudicell et al., 2010; Schaumburg et al., 2012a]. Readers are referred to excellent reviews of infectious diseases of free-living great apes; however, methods for fecal and noninvasive sampling for the screening of a variety of pathogens [Calvignac-Spencer et al., 2012; Gillespie et al., 2008; Leendertz et al., 2006]. Accordingly, there are several molecular methods that may be applied to such samples and be useful in the detection of tuberculosis infection (Table II).

The collection of saliva samples of great apes from what is commonly referred to as “wadges,” or masticated clumps of forest food, has found use in genetic research of free-living great apes and has more recently been employed in noninvasive disease screening [Inoue et al., 2007; Schaumburg et al., 2012a; Shimada et al., 2004; Smiley et al., 2010]. Saliva samples from animals with clinical signs of disease could be utilized for the detection and genotyping of M. tuberculosis through culture and/or commonly employed techniques such as IS6110 PCR-RFLP, spoligotyping, or mycobacterial interspersed repetitive unit-variable number tandem repeat (MIRU-VNTR) genotyping [Sankar et al., 2011; Wilbur et al., 2012]. These techniques are useful in distinguishing M. tuberculosis from infection with other MTC strains. In human medicine, mannose-capped lipoarabinomannan (LAM), a cell wall component of pathogenic mycobacteria, has been utilized as a urine biomarker of tuberculosis infection [Hamasur et al., 2001]. The utility of this biomarker in the diagnosis of infection in humans has been limited by low sensitivity and specificity, although it has shown greater accuracy in patients co-infected with HIV [Peter et al., 2010]. The usefulness of LAM in the detection of tuberculosis in non-human primates has yet to be determined. Urine collection is a realistic option for non-invasive sample collection, having been used in other disease surveys; thus, it is reasonable to consider LAM as a possible biomarker for non-invasive tuberculosis detection in great apes [Leendertz et al., 2006]. Fecal samples are the most readily available and easily attainable biological samples of free-ranging great apes. The detection of fecal antibodies against pathogenic organisms has not been widely utilized for disease screening in primates; however, methods for fecal antibody detection have proven successful for the non-invasive detection of Simian Immunodeficiency virus and Simian Foamy virus in wild chimpanzees [Keele et al., 2009; Liu et al., 2008]. Given the development of a detectable humoral immune response to tuberculosis in primates, the detection of anti-tuberculosis antibodies in feces may be a feasible option for diagnosis [Lin et al., 2008; Lyashchenko

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<td>Saliva</td>
<td>Culture and genotyping</td>
<td>Infected individual must be infectious for the detection of organisms by culture or PCR, thus latent infection may go undetected. Possible low sensitivity associated with antibody detection</td>
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<td>Mycobacterial PCR</td>
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<td>Antibodies</td>
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<td></td>
<td>LAM</td>
<td>Low sensitivity and specificity in humans</td>
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<td>Urine</td>
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<tr>
<td>Feces</td>
<td>Culture and genotyping</td>
<td>Infected individual must be infectious for the detection of organisms by culture or PCR, thus latent infection may go undetected. Possible low sensitivity associated with antibody detection; antibodies present in swallowed sputum may be denatured in the stomach</td>
</tr>
<tr>
<td></td>
<td>Mycobacterial PCR</td>
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<tr>
<td></td>
<td>Antibodies</td>
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</tr>
</tbody>
</table>

LAM, lipoarabinomannan.

Am. J. Primatol.
et al., 2007]. Hence, exploration into fecal antibody detection may be warranted as another option for non-invasive tuberculosis screening in great apes. Alternatively, fecal culture or molecular detection of mycobacterial DNA in the feces of great apes offers another opportunity for the diagnosis of disease. Recent studies among humans with active pulmonary tuberculosis reveal approximately 50% sensitivity and 100% specificity for the detection of *M. tuberculosis* by stool culture, and even higher sensitivity using molecular detection (e.g., IS6110 PCR-RFLP) [Cordova et al., 2010; El Khéchine et al., 2009]. Therefore, culture and/or PCR may be a useful approach to pathogen detection in the feces of great apes.

A major limitation to the detection of tuberculosis infection by any of these methods is the latent stage of disease, in which case animals are not infectious and detection of the organism and immune response is often more challenging [Lin et al., 2008]. Alternatively, given the utility of these non-invasively collected specimens for potential disease screening of other pathogens, it is advantageous to move toward the development and validation of such methods. Certainly, as these methods for non-invasive tuberculosis detection improve and become more widely available, a more comprehensive assessment of tuberculosis status among great ape populations (e.g., disease-free or not) can be undertaken through ante-mortem population surveillance or monitoring.

**Directions for Future Research and Mitigation of Tuberculosis Risk**

Understanding and/or mitigating the risk of tuberculosis for the conservation of great ape populations requires an ecosystem health approach. *M. tuberculosis* is a human pathogen, and there is evidence of high prevalence among humans residing in close proximity to great ape habitats across their home ranges. Better estimates and understanding of control measures for this disease in local human populations are needed for accurate estimation of risk to great ape populations with which they have contact. Thus, it is essential to develop partnerships among conservation managers and those involved in human health at local and non-governmental levels. Given the evidence of human respiratory diseases in great ape populations, it can be concluded that the necessary contacts already exist between humans and great apes for successful disease transmission. Whether these contacts are sufficient for tuberculosis transmission has yet to be determined. Furthermore, the role of the environment in the transmission of such pathogens remains unknown. Accordingly, epidemiological research into routes of transmission of known human pathogens affecting great ape populations are needed not only for protecting against specific disease, but also in understanding and potentially predicting opportunities for *M. tuberculosis* transmission within these ecosystems. Certainly, the most promising means of protecting great apes from *M. tuberculosis* is by improving the healthcare infrastructure among local human communities, thereby reducing the burden of human tuberculosis in these regions.

*M. tuberculosis* is, unfortunately, not the only mycobacterial pathogen for which great apes may be at risk of infection. *M. bovis*, a known pathogen of domestic livestock and wildlife, not only causes disease in humans, but has also spilled over into free-ranging monkey populations. Thus, understanding of the risk and prevention of *M. bovis* infection in great apes also requires efforts in the area of bovine tuberculosis. There is a significant need for regulation, surveillance, and control of bovine tuberculosis in developing countries, as well as education on the zoonotic potential of this pathogen. Endeavors to meet such objectives could significantly reduce the impact of this disease for humans and their livestock, as has been observed in developed countries, as well as eliminate a disease risk to great ape populations. Until these needs are met, however, estimates of *M. bovis* levels in local livestock populations and potential routes of transmission are necessary to characterize this disease risk to great ape populations.

*M. tuberculosis* is an old pathogen, originating in Africa [Cosma et al., 2003; Gagneux, 2012]. This pathogen’s co-evolution with its human host is complex and there is much we are still learning about variability of infection, host response, distribution, and genetic and functional diversity [Cosma et al., 2003; Gagneux, 2012]. Likewise, similar observations of variations in infection and host response among primates have yet to be fully explored. Combined with historical limitations of diagnosing tuberculosis infection in free-ranging primate species, it cannot be known with certainty that this pathogen is not already present in these populations nor the full extent to which other MTC members (such as “Chimpanzee bacillus,” reported by Coscolla et al.) infect these populations [Coscolla et al., 2013]. The impact of tuberculosis and the dynamics of co-infection with other diseases (e.g., SIV) on the persistence of free-ranging primate populations cannot be fully assessed without the development and employment of sensitive and reliable means for detecting infection and characterizing the pathogen.

As long as tuberculosis continues as a significant human and livestock disease, there is inherent risk of transmission to remnant great ape populations with which there is human contact. Accordingly, just as protection of these populations against threats of further habitat loss and poaching is ensured through conservation and research activities, we must endeavor to enhance our understanding and mitigate
the risks of tuberculosis and other human and domestic animal pathogens that equally threaten the persistence of these populations.

ACKNOWLEDGMENTS

Exploration into the risk of tuberculosis for habituated great apes is supported in part by the Zoetis/Morris Animal Foundation Veterinary Research Fellowship, the Consortium on Law and Values in Health, Environment & the Life Sciences of the University of Minnesota, the Ulysses S. Seal Conservation Fund of the Minnesota Zoo, the USDA-NIFA Specials grant on bovine tuberculosis, and the Veterinary Population Medicine Department of the University of Minnesota’s College of Veterinary Medicine. The authors also thank the two American Journal of Primatology reviewers who provided insightful and thought-provoking comments and recommendations that contributed to the development of a more complete manuscript. This manuscript adhered to the American Society of Primatologists’ Principles for the Ethical Treatment of Primates.

REFERENCES


