Tuberculosis Infection in Free-Ranging Long-Tailed Macaques through Social Network and Modeling

By

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Abstract

This dissertation addresses the escalating threat of anthropozoonosis at human-wildlife interfaces by investigating the social dynamics of disease transmission among wildlife populations, focusing particularly on long-tailed macaques (*Macaca fascicularis*) inhabiting human-wildlife interface areas. Tuberculosis (TB) serves as the model infectious disease due to its high prevalence in Southeast Asia, air-borne transmission and its zoonosis nature. Although concerns about disease risks to these macaques have been raised, the role of individual variation, encompassing social network attributes and human exposures, has remained unexplored. To address these questions, this project utilizes non-invasive techniques for sample collection from a population of free-ranging macaques in Thailand. I adopt a network approach to examine the intricate relationship between social attributes and TB infection status. Furthermore, an epidemiological model, Susceptible-Exposed-Infectious-Recovered-Susceptible (SEIRS), is integrated to monitor changes in individuals' disease states and explore hypothetical scenarios of disease spread within social networks, with parameters tailored to each individual.

Chapter One investigates the factors driving pathogen infection by identifying infected animals and examining how sociodemographic attributes, combined with interactions with conspecifics, humans, and responses to stress and sickness, influence TB infection patterns within social groups. Notably, it reveals that the likelihood of TB infection increases among individuals with high human interaction and those engaging in less grooming activity.

Chapter Two explores the influence of social network positions on TB transmission. By implementing a social network approach to locate infected individuals, this chapter explores the interplay between contact-transmission and social buffering. It highlights the significance of

individual macaques' social network positions in their infection status, emphasizing that monkeys with fewer grooming interactions and living periphery are more likely to have TB.

Chapter Three employs mathematical modeling within the network to investigate transmission dynamics and the persistence of TB, taking into account variations in transmissibility and latency periods. SEIRS models reveal that over half of the population remains in the latent stage of TB infection. It elucidates that social buffering, specifically the adjustment of the latency period from latency to active TB, plays a pivotal role in explaining the presence of infected individuals in the social network periphery. In contrast, adjusting transmissibility fails to accurately represent observed relationships in this population.

Overall, this dissertation aims to uncover the social and demographic factors that influence the acquisition and transmission of TB among free-ranging long-tailed macaques inhabiting human-wildlife interface areas. Understanding the attributes of social network components in wildlife populations at the human-wildlife interface contributes to mitigating infectious disease transmission, reducing zoonotic risks, and promoting the well-being of both humans and wildlife. These insights play a crucial role in clarifying steps to prevent potential future pandemics.

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Table of Contents

General Introduction

Infectious disease plays a major role in the social lives of humans and other group-living animals. An increase in the emergence of novel pathogens and the spread of existing ones have been driven by many factors, including environmental change, human population growth, global travel, and interactions between humans and animals (Hassell et al., 2017; Townsend et al., 2020). Recently, the COVID-19 pandemic has sparked interest in the study of disease transmission in humans and other animals that can carry similar diseases (Gryseels et al., 2020). The COVID-19 pandemic has emphasized the importance of studying the transmission dynamics of zoonotic respiratory microbes in humans and other animals (Lappan et al., 2020).

While animals are integral to human existence, as companions, livestock, or wildlife, these interactions and shared interfaces between humans and animals pose the risk of zoonosis spillover, i.e. the transmission of infectious diseases from other animals to humans (Daszak et al., 2000). In fact, these interfaces can constitute 'hotspots' for zoonosis to spillover between species (Bird & Mazet, 2018; Plowright et al., 2017). For instance, human contact with wild animals for bushmeat has been directly linked to the emergence of several known high-consequence zoonoses, including monkeypox (Quiner et al., 2017), ebolaviruses (Judson et al., 2016; Ordaz-Németh et al., 2017), simian retroviruses (Gessain et al., 2013; Wolfe et al., 2005), and coronaviruses (Jacob et al., 2020). Similarly, the expansion of animal farms into overlapping areas with wildlife has resulted in several examples of zoonotic disease emergence in both wild and domestic animals. Examples include tick-borne bunyaviruses in livestock (Liu et al., 2014), henipaviruses in pigs and horses (Croser & Marsh, 2013), and coronaviruses in camels (De Wit et al., 2016).

However, control of disease transmission in livestock and wildlife is constrained by the lack of dependable science based on addressing transmission dynamics and behavior of host animals (Cross et al., 2004; Maréchal et al., 2011a). The unpredictable nature of zoonosis poses a huge threat to humans, livestock, wildlife and global biodiversity (Daszak et al., 2000). In the case of SARS-CoV-2, the infectious virus can spillback (or reverse spillover) from humans to animals, mutate, and then spread back to humans (bidirectional transmission) (Oude Munnink et al., 2021). When a new strain of COVID-19 was found in people within a mink farm in Denmark, more than 17 million farmed minks were culled to prevent appearance of new strains of COVID-19 (Frutos & Devaux, 2020). More basic knowledge is needed to reduce unnecessary culling, improve management of public health risks, and mitigate existing infectious zoonotic diseases.

Nonhuman primates (hereafter primates) are good models to understand the ecological and social factors that affect zoonosis, as they share close evolutionary histories, overlapping ecological space, and a similar physiology with humans (Morse et al., 2012). Many primates are known for having several comparable and shared diseases with humans such as malaria (Sato et al., 2019), HIV/SIV (Peeters et al., 2002), Herpes B (Tischer & Osterrieder, 2010), and tuberculosis (Bushmitz et al., 2009). As with humans, the acquisition and transmission of these infectious diseases among primates may be influenced by a myriad of factors, including: social interactions with conspecifics (Drewe et al., 2011a; Romano et al., 2016a), ecological conditions or contaminants (Chiyo et al., 2014), exposure from humans and other animals (Wilbur et al. 2012a), and intrinsic qualities such as an individual's physiological stress-levels or immune function (Maréchal et al., 2011b; Munck et al., 1984). Most of what we know regarding primate infectious disease ecology focuses on the acquisition and fecal-oral transmission of

gastrointestinal pathogens such as protozoa (Freeland, 1979), nematodes (MacIntosh et al., 2012; McGrew et al., 1989) and helminth parasites (Friant et al., 2016; Rimbach et al., 2015a). In comparison, there are fewer empirical studies that implement network approaches to investigate the socioecology of zoonotic respiratory pathogen transmission at human-primate interfaces (Rushmore et al., 2017; Sandel et al., 2021a; Wolfe et al., 2005).

Macaques are one of the most geographically widespread and behaviorally flexible primate species that live in proximity to human communities, and interaction around potential macaque food sources results in an exceptionally high rate of primate-human interaction (Malaivijitnond & Hamada, 2008a). Previously, concerns have been raised about increased disease risk to macaques owing to extensive interactions and space-use overlap between humans and macaques (Fuentes, 2006; Jones-Engel et al., 2006). Interacting with humans, especially in aggressive contexts, can increase stress (Maréchal et al., 2011b), which may also suppress the immune system and increase macaques' susceptibility to disease (Munck et al., 1984). When close contact interactions (such as climbing, or mucosal splashing) occur, both macaques and humans are potentially susceptible to infectious agents, especially respiratory pathogens (Fuentes, 2006; Jones-Engel et al., 2006). Outbreaks of respiratory pathogens often occur quickly and unpredictably, making it challenging to record social contact and disease incidence data, especially in wildlife (Sandel et al., 2021a). Therefore, little is known about demography and the types of interactions (ecological/social) among primates that lead to their acquisition and transmission.

This project focuses on the respiratory disease of Tuberculosis (TB), due to its high prevalence and mortality risk in human and primates of Southeast Asia (Warit et al., 2020a). When an infected individual releases tiny saliva droplets, they may disperse the bacteria known

as *Mycobacterium tuberculosis* complex (MTBC) into the air, potentially exposing susceptible individuals. Exposed individuals who fail to clear all bacteria can progress to the status of latent tuberculosis infection, in which bacteria remain in the body in an inactive state and cause no symptoms, or the active stage. People in latent stage are not infectious and cannot spread TB infection to others. In some cases, MTBC overcome the defenses of the immune system and begin to multiply, resulting in the activation from latent to active TB disease (World Health Organization, 2022). Individuals with active TB disease are considered infectious and may spread MTBC to other susceptible people through coughing or sneezing (de Martino et al., 2019). Due to the challenges associated with testing for latent TB, including limitations in available resources, cost, and technical expertise, many countries prioritize testing for active TB to identify and treat cases that pose an immediate risk of transmission (Esmail et al., 2014).

Macaques have been widely used for TB research (Capuano et al., 2003a; Flynn et al., 2003a), however, very few empirical studies have tried to understand how TB naturally occurs in primates, even with several outbreaks of TB having been reported in primate colonies and zoological gardens (Gong et al., 2017; Mätz-Rensing et al., 2015). TB is the most frequently reported infectious disease of captive primates living in close contact to humans, and increases in TB infections among free-ranging macaques occur in areas of frequent human contact and high human TB prevalence (Wilbur et al. 2012b). However, the specimen collected from this method was invasive as they needed to catch and anesthetize macaques to collect specimens. A noninvasive technique to collect samples, such as using a rope bait method to collect pathogens inside the oral cavity (Meesawat, Aiempichitkijkarn, et al., 2023) or analyzing samples from recently dropped feces (Wolf et al., 2015), is suggested to incorporate behavioral observation into epidemiological studies of TB among free-living primates (Meesawat, Warit, et al., 2023).

While infection with MTBC is the definitive cause of TB, there are many factors that can make some individuals more susceptible to the disease such sex, age, and social status as well as their social activities. Additionally, several conditions associated with poor immunity can indicate a greater risk of developing TB. In humans, for example, people of low socioeconomic status are both more likely to contract TB and to be more severely affected by the disease (Narasimhan et al., 2013a). Infants are at higher risk of contracting TB infection and expressing active disease as they have less immunological protection against conversion from latent to active tuberculosis. Similarly, elderly people also represent a population at a heightened risk for developing TB owing to a combination with other medical conditions and age-related immunosuppression (Byng-Maddick & Noursadeghi, 2016).

For social animals living in tight-knit groups like macaques, and for an infectious disease like TB, an interesting question is why some group members but not others become infected once an infectious disease enters a social group. This phenomenon raises questions about the role of sociodemographic attributes and how they might interact with macaque's interactions with both conspecifics (members of the same species) and heterospecifics (such as humans). Additionally, factors like stress-related responses and behaviors associated with sickness can further complicate the situation. In Chapter One, I explored how these sociodemographic attributes, potentially in combination with the macaques' interactions with conspecifics and humans, as well as their responses to stress and sickness, influence the patterns of TB infection within this social group.

Epidemiological models traditionally assumed that animals within social groups interacted randomly (Bansal et al., 2007a). However, social animals, especially those living in complex social groups like macaques, differ in both the number and extent of their interactions

with conspecifics (Craft, 2015a). Social network analysis has emerged as a valuable tool to capture this heterogeneity in interactions between individuals (Lazega et al., 1995a). Over the past decade, it has been extensively employed to study how infectious agents spread through such groups (Drewe et al., 2011a; MacIntosh et al., 2012; Sandel et al., 2021a; Silk et al., 2019).

In the context of disease transmission, an individual's network position reflects their susceptibility to disease or social response to infection, mediated through various factors including individual attributes, social connectedness, or disease avoidance. These social attributes play a crucial role in determining the likelihood of contracting TB, as they define the nature, frequency, and duration of interactions among different individuals. Moreover, within a population, not all animals are equally responsible for transmitting diseases. The majority of infected individuals contribute to relatively few transmission events, while some super spreader individuals act as hubs and spread a disproportionate number of infections (Lloyd-Smith et al., 2005; R. A. Stein, 2011). Additionally, certain individuals can act as bridges between different parts of a network, such as between two social groups, potentially facilitating the spread of infection (Silk et al., 2019). This dynamic interplay between social attributes, network position, and disease transmission underscores the complexity of disease dynamics within animal populations.

In Chapter Two, I explored how an individual's centrality (level of connectedness within the network) is an important determinant of infection status. That is, I locate infected individuals in a social network. On the one hand, increased connections may lead to greater chances of infection from pathogens via contact-mediated transmission (Drewe & Perkins, 2015), making infectious disease acquisition a major cost of social living. That is, high social connectedness puts individuals at greater risk for acquiring pathogens via a contact-mediated transmission

(Romano et al., 2016b). For example, meerkats (*Suricata suricatta*) that groomed others most were more likely to become infected with TB (Drewe et al., 2011b). Central brown spider monkeys (*Ateles hybridus*) in the contact network had greater gastrointestinal parasite species richness than less central monkeys (Rimbach et al., 2015b). Japanese macaques (*M. fuscata*) generally have a higher risk of infection if they are better connected (more central) in the network (Romano et al., 2016b).

On the other hand, social buffering—having more social ties can mitigate stress to generate positive health outcomes (Cobb, 1976; Young et al., 2014) – is well-documented in many strongly bonded societies like macaques (*Macaca* sp.), baboons (*Papio* sp.) and humans. In primates, grooming (an affiliative social interaction) may be exchanged among group members for access to social support (Seyfarth, 1977), and is also known to lower circulating levels of glucocorticoids by reducing activation of the hypothalamic-pituitary-adrenal (HPA) axis (Young et al., 2014).

Therefore, a dilemma exists where individuals with high connectivity could simultaneously be less and more likely to be infected than individuals with low connectivity. Despite the conservation implications and seriousness surrounding this topic, there are surprisingly few studies that analyze these effects of social connections on primate health using social network approaches (Balasubramaniam et al., 2016). To better understand how social connections impact disease-related health outcomes, it is imperative to assess the effects of contact-mediated transmission and social buffering, particularly indirect social connections through which group members may elicit social support, on the risk of acquiring infectious agents.

Over the past decade, network compartmental modeling has emerged as a valuable approach for providing essential insights into disease transmission dynamics and proposing scientifically informed interventions that might be otherwise challenging to explore (Craft & Caillaud, 2011a). For instance, studies have revealed that grooming, as opposed to aggression, is more likely to be correlated with *Mycobacteriam bovis* transmission in meerkats (Drewe et al., 2011). More central individuals transmit infections more rapidly to a larger number of subjects, but they also become infected more quickly themselves compared to less central individuals (Romano et al., 2016a). Additionally, in vaccination simulations, targeting the most central chimpanzees has proven effective in reducing the number of vaccines required to prevent an outbreak compared to random vaccinations (Rushmore et al., 2014a). These findings highlight the valuable insights provided by network compartmental modeling in understanding and managing disease transmission within social animal groups.

The classical susceptible-infectious-recovered (SIR) model is one of the most basic compartmental models (Kermack & McKendrick, 1991). It categorizes individuals into distinct compartments based on their infection status. Initially, all individuals are considered to be in the "Susceptible" state, and as the model progresses, they transition to the "Infectious" state and eventually to the "Recovered" state based on specified parameters. Consequently, traditional SIR models enable predictions regarding the number of individuals who are susceptible to infection, those actively infected, and those who have recovered from infection at any given time (Cooper et al., 2020; Tolles & Luong, 2020).

In the context of TB, I use a more advanced model called SEIRS (Susceptible-Exposed-Infectious-Removed-Susceptible) (Bjørnstad et al. 2020; Erinle-Ibrahim et al. 2021). This model is designed to consider latent TB period, during which individuals are infected but cannot yet

spread the disease, as well as the potential for reinfection after recovery. These aspects are critical for understanding why TB continues to persist in some populations. In Chapter Three, I introduce a novel approach by incorporating diverse transmissibility and latency periods, thus providing a more realistic representation of individual differences in TB dynamics within complex social networks. Through the application of these advanced models, my overarching goal is to shed light on the enigmatic nature of disease endemicity and reveal the intricate buffering effect of TB within such networks.

My research aims to connect behavioral observation, network analysis, and epidemiological mathematical modeling to explore the dynamics of TB transmission among a population of urban long-tailed macaques (*M. fascicularis*) in Thailand. Through this interdisciplinary approach, my objective is to provide a holistic and in-depth understanding of disease spread within intricate social networks. By combining these diverse methodologies, I seek to reveal the nuanced interactions and factors that influence TB transmission in this population, ultimately contributing to a more comprehensive understanding of disease dynamics within the context of wildlife and human interactions.

Chapter 1: Assessing the Sociodemographic Factors Associated with Tuberculosis Occurrence among Free-Ranging Long-Tailed Macaques

Introduction

One of the major challenges for conservation biologists is evaluating the myriad factors that influence infectious disease risk at human-wildlife-livestock interfaces (Hassell et al., 2017; Townsend et al., 2020; Wiethoelter et al., 2015). The COVID-19 pandemic has highlighted the danger of zoonotic diseases originating from these interfaces, emphasizing the importance of assessing disease risk among both wildlife and humans for conservation, management, and public health (Gryseels et al., 2020; Lappan et al., 2020). This is very challenging since infectious disease risk is a subtle and hidden outcome of human-wildlife interactions that can go unnoticed in both people and wildlife unless we understand the ecological, evolutionary and behavioral underpinnings of such risk (Barua et al., 2013; Daszak et al., 2000). This complexity is particularly amplified in urban or peri-urban locations, where dense populations of co-existing humans, wildlife, and livestock frequently exchange infectious agents that may exhibit prolonged dormant phase or exist in benign or non-infectious states within certain individuals and species (Hassell et al., 2017).

Despite its significance for both conservation and public health, critical gaps remain in our understanding of the ecology of infectious agents at human-wildlife-livestock interfaces. One notable gap is the disproportionate number of studies that primarily focus on investigating the prevalence of zoonotic agents in humans, with comparatively fewer studies evaluating the transmission and prevalence of zooanthroponotic agents that enter wildlife populations from humans (Fagre et al., 2022). Conducting more quantitative assessments of the latter would be

vital from a conservation standpoint, particularly because zooanthroponotic agents can have diverse impacts on wildlife. For instance such agents, depending on the biology and behavior of the host species, can persist in a benign or asymptomatic state in wildlife that may act as natural reservoirs (Mackenzie & Jeggo, 2013), may enter into and spread through otherwise uninfected but more vulnerable wildlife populations (Sokolow et al., 2019), and/or cause symptomatic illness, disease and mortality in vulnerable wildlife populations (Balasubramaniam et al., 2022; Köndgen et al., 2008).

Infectious diseases caused by respiratory pathogens often pose significant challenges due to their rapid and unpredictable outbreaks (Sandel et al., 2021a). This is particularly true for TB, which is caused by the MTBC. MTBC can spread through respiratory droplets produced when an infected individual coughs or sneezes. It primarily affects the lungs through coughing and respiratory transmission. The World Health Organization has set a strategic plan to eradicate TB from the world by 2030. However, there is a growing concern that TB in wildlife could pose a serious threat to global health (World Health Organization, 2022). If TB were to spread from wildlife to humans, there could be concerns about the potential for a widespread outbreak. This situation draws parallels to the challenges we have faced with COVID-19 (Akhtar et al., 2021; Sarınoğlu et al., 2020), highlighting the complexities of disease transmission and the importance of robust public health measures in preventing and managing such outbreaks.

In particular, the detection and prevalence of TB in some urban and peri-urban wildlife species emphasizes the need for further research into the ecology of TB in other, urban-dwelling settings (Delahay et al., 2002). For instance, European badgers (*Meles meles*) in urban areas of the UK serve as natural reservoirs for TB and are a cause for concern. Studies have shown that TB-positive badgers are socially isolated from their own groups but are more important for the

flow of infection between social groups (Weber et al., 2013). In France, red deer (*Cervus elaphus*) are susceptible to *M. bovis* and can transmit the disease to livestock and humans (Michelet et al., 2019). These findings highlight the importance of conducting similar assessments of the detection and causal factors of MTBC infection and prevalence in other urban wildlife.

In particular, our understanding of TB in wild primate populations remains limited, despite TB posing a significant threat to both human and primates (Flynn et al., 2003b; Scanga & Flynn, 2014). Addressing this gap in the literature is especially critical, since primates share both close evolutionary histories (Perelman et al., 2011) and increasing ecological niche spaces with humans (Sinha & Vijayakrishnan, 2017). Consequently, primates pose a highly significant TB threat to otherwise uninfected humans, livestock and other wildlife (Thapa et al., 2017). Assessing the ecology of MTBC infection among free-living primates in anthropogenically impacted areas can have ecosystem-wide implications for conservation and human-wildlife conflict management (Wilbur, Engel, & Jones-Engel, 2012).

Although macaques have been widely used for nonclinical TB research, there exist few empirical studies aimed at understanding how TB naturally occurs in wild macaques. This gap is despite several outbreaks of TB having been reported in macaque colonies and zoological gardens (Gong et al., 2017; Mätz-Rensing et al., 2015). TB is the one of the most frequently anthropozoonotic reported infectious diseases of primates living in close contact to humans (Wilbur, Engel, & Jones-Engel, 2012). Indeed, we know that TB prevalence is generally higher among free-ranging macaques that occur in areas of more (compared to less) frequent human contact and high human TB prevalence (Wilbur, Engel, Rompis, et al., 2012a). Previously, concerns have been raised about increased disease risk to macaques owing to extensive

interactions and space-use overlap between humans and macaques (Fuentes, 2006; Jones-Engel et al., 2006). Interacting with humans, especially in aggressive contexts, can increase stress (Maréchal et al., 2011b), which may also suppress the immune system and increase macaques' susceptibility to disease (Munck et al., 1984). When close contact interactions occur, such as climbing or mucosal splashing, there is a potential risk of infectious agents being transmitted between both macaques and humans, especially respiratory pathogens. While instances of TB transmission from monkeys to humans remain undocumented, the potential risks have garnered significant attention, emphasizing the importance of further research and precautionary measures to address the issue (Fuentes, 2006; Jones-Engel et al., 2006).

Sample collection and screening wild populations for TB, however, presents a challenge because collected specimens should be from the organs related to the respiratory tract. The invasive nature of some specimen collection methods, such as catching and anesthetizing wild animals, may lead to altered behavior in response to sampling (Camacho et al., 2017). That is, repeated invasive procedures can limit the incorporation of behavioral aspects in TB research among wildlife. Consequently, most research on wild primates has been limited to assessing TB detection and population-wide prevalence (Meesawat, Warit, et al., 2023; Wilbur, Engel, & Jones-Engel, 2012), without evaluating the demographic and socio-ecological factors that might influence such prevalence (Nunn, 2012). In general, the likelihood of acquiring socially transmitted infectious agents may be influenced by individual attributes like individuals' sex, age and dominance rank (Cross et al., 2009); emergent aspects of their social behavior, including grooming and agonistic interactions with other individuals (Drewe et al., 2011); the frequency of interactions between wild animals and humans (Balasubramaniam et al., 2022); and individuals' health indicators that may encompass factors like physiological or behavioral indicators of stress

and immune function (Kohn et al., 2016). In primates, empirical assessments of such effects have largely been conducted for gastrointestinal infectious agents from non-invasively collected feces, but less so for respiratory pathogens. To address this limitation, noninvasive sampling techniques have been proposed (Gillespie et al., 2008), like using rope bait to collect pathogens from the oral cavity (Meesawat, Aiempichitkijkarn, et al., 2023; Simons et al., 2012) or analyzing samples from freshly dropped feces that might still be conducive to detecting respiratory pathogens (Wolf et al., 2015). Since MTBC bacteria that cause TB are shed in the sputum and the animals subsequently swallowed and excreted the MTBC in feces during active infection. The fecal MTBC shedding DNA detection method, utilizing PCR amplification of IS*6110*, has been developed and validated for free-living primate such as chimpanzees (*Pan troglodytes*), baboons (*Papio anubis*) (Wolf et al., 2016), and long-tailed macaques (Meesawat et al., 2023b). Incorporating these noninvasive methods enable epidemiological studies of TB among free-living primates, while also recording their natural behavior (Mendoza et al., 2020). Thus, these techniques present an opportunity to study TB transmission dynamics while preserving natural behavior in a wild population of primates. This approach is especially applicable to primates and protected wild species where securing permissions for invasive procedures for logistic or ethical reasons.

For social animals living in tight-knit groups like macaques, and for a respiratory infectious disease like TB, I addressed the question as to why some group members, but not others, become infected once an infectious disease enters a social group. Long-tailed macaques live in multi-male multi-female social groups of varying sizes, in which mature males disperse and emigrate from their natal groups, females remain in their natal group for life (Van Noordwijk & Van Schaik, 1985) and maintain long-term affiliative relationships with other females in their

group (Wrangham, 1980). High-ranking male macaques generally have higher tendency to interact with humans (Balasubramaniam et al., 2020). Such behavioral patterns could lead to varying risks of infections among long-tailed macaques. For example, a study of captive long-tailed macaques showed that low ranking individuals had higher rates of adenovirus infection (Cohen et al., 1997). Moreover, mathematical models showed that aggregations around anthropogenic factors could make macaques more vulnerable to zooanthroponotic outbreaks than their social structure (Balasubramaniam et al., 2022).

While TB has been found in wild macaques at difference prevalence (Meesawat, Warit, et al., 2023), there exists little research on the animal and environmental variables that might influence such prevalence. More specifically, aspects of inter-individual differences in macaque demographics or social behavior that might put individuals at risk of acquiring TB are likely multifaceted in nature, and not well understood. Current understanding suggests that demographic factors such as sex (O'Brien et al., 2002) and age (Jolles et al., 2005; Joly & Messier, 2004) are among the important risk factors for TB status across mammals. Therefore, the overarching objective of this study was to address this knowledge gap by using non-invasive method to explore how individual demographic attributes and socio-ecological factors and their relationship to human-macaque interactions influence active TB status.

Hypotheses and predictions

H1 Human Interaction Hypothesis: Previous studies have revealed that frequent contact with humans may increase the likelihood of acquiring anthropozoonotic pathogens in wildlife (Jiang et al., 2023). Given this, I predicted that higher frequencies of human-macaque interactions would influence a greater likelihood of having MTBC in long-tailed macaques.

H2 Conspecific Interaction Hypothesis: Engaging in more social interactions increases the likelihood of individuals being exposed to infectious agents and consequently raises their risk of contracting MTBC (e.g. meerkats (*Suricata suricatta*): Drewe et al. 2011; Patterson et al. 2017; badgers: Rozins et al. 2018; Weber et al. 2013) Therefore, I predicted that macaques that engaged in more social grooming activity with their conspecifics are more likely to acquire MTBC.

H3 Sickness-related Hypothesis: More recent research has begun to establish links between aspects of animal sociality and health outcomes like stress and immune response, and in turn their vulnerability versus resistance to infectious agents (Cohen et al., 2015; Hennessy et al., 2009; Müller-Klein et al., 2019; Snyder-Mackler et al., 2016; Sweeny & Albery, 2022). In particular, individuals who tend to have lower immunity against infectious diseases, due to low rank certainty (Vandeleest et al., 2016), age-related immunosuppression (Mätz-Rensing et al., 2015), or stress (Dutta & Karakousis, 2014), are at a heightened risk for developing diseases. Yet such risk may be offset by increasing affiliative social interactions, and consequently the establishment and maintenance of strong long-term social bonds (Balasubramaniam et al., 2016; Müller-Klein et al., 2019; Young et al., 2014). In accordance with this hypothesis, I predict that macaques with demographic and social characteristics, which are closely associated with immunosuppression, are more susceptible to TB infection. These characteristics may include older age, low rank certainty, high involvement in agonistic behavior, low grooming activity, and high frequency of stress-associated behaviors, such as self-scratching (Troisi et al., 1991).

Materials and Methods

Study site and subjects

The study was conducted in Thailand, which is among the highest of countries with TB-related disease burden worldwide (World Health Organization, 2022). Thailand has an abundance of long-tailed macaque populations of different sizes, and in varying extents of overlapping habitually with humans and anthropogenic landscapes (Malaivijitnond & Hamada, 2008b). Field work was conducted at Wat Kao Thamon (WKT), Phetchaburi Province (13° 02' N, 99° 57' E). WKT is a Buddhist temple surrounded by forest, mountain, pond, school, and rice field, where there are large social groups of free-ranging long-tailed macaques that are habituated to people. The resident monks provide them with food on a daily basis. Additionally, visiting humans often bring offerings of human foods, such as coconuts, rice, and other tropical foods; however, there have been observations of these animals engaging in aggressive behaviors toward humans. The survey in 2008 estimated that there are four groups of approximately 500 macaques in total (Malaivijitnond & Hamada, 2008b). According to a survey conducted in July 2021, there were three groups of approximately 400 free-ranging macaques. The largest group (N = ~200), referred to as the main group, utilized an area of about 0.1 km^2, primarily within the temple area and forest, but occasionally venturing to the mountain, pond, and rice field. The second group (N = ~50) resided near a school. The third group (N = ~150) inhabited the mountain area. The second and third groups, however, are not habituated and, thus, are not part of the study.

Behavioral observation and sampling approach

For this study, I focused on the main group, which comprised 149 adults and around 50 juveniles. My research team conducted behavioral observations on all adult individuals for a period of six months from September 2021 to February 2022. Specifically, we collected data on

Samsung Galaxy Tablets using customized data forms created in the HanDBase® application (Kaburu et al., 2019). Four observers (KKO, THU, WKR, and NAI) collected data for 6.5 h/day on Monday to Friday from 10:00–12:00 and 13:00–17:30. Prior to data collection, observers passed inter-observer reliability tests using Cohen's kappa at a cut-off of ≥ 0.85 (Kaburu et al., 2019). We collected the following types of data listed below, which included aspects of macaques' exposure to anthropogenic factors in their environment as well as their social interactions with their conspecifics and humans (see Supporting Information: Appendix S1 Ethogram for a full ethogram):

(i) Behavior sampling (Martin & Bateson, 2007): We recorded all instances of dyadic social interactions, specifically social or allogrooming, agonistic interactions that involved either aggression or submissive responses, instances of mating, and instances of interacting with humans. As behavioral indicators of sickness, we also recorded all instances of coughing observed during data collection (149 animals). For each dyadic interaction, the identities of the initiator and recipient macaque, and their specific behavior(s) were recorded.

(ii) Focal sampling (Altmann, 1974): A subset of identified animals who had shown frequent conspecific-interactions, during the survey period, were selected for focal follow (101 out of 149 animals; 67.79%). Focal animals were followed for ten-minute periods a day, in a pre-determined pseudo-randomized sequence. Within each focal session, we recorded, in a continuous manner, instances of agonistic interactions, instances of self-scratching, instances of mating, and durations of time spent by focal animals giving or receiving grooming. At the end of the observation period, three individuals were dropped from the analyses due to insufficient focal observations (range: 6.93-8.62 hours), leaving 98 focal individuals (57 males and 41 females) with more than 10 hours of observation (range: 10.24-14.44 hours).

(iii) Point-time scan (details in Kaburu et al. 2019): During a 10-minute focal observation session, we paused continuous data collection once every two minutes in order to record six point-time scans to observe the focal animal's main activity (i.e. whether subject was interacting with humans, interacting with conspecific, eating anthropogenic food, eating natural food, locomoting, or resting), the density levels of conspecific (i.e. low: 0-11 monkeys, medium 11-20 monkeys, high: more than 20 monkeys) within 20 meters of the focal animal. Additionally, we recorded the presence of dogs, humans, and identity of the conspecifics that were within the body length of the focal monkey.

Estimations of demographic, social and behavioral measures

Demographic characteristics: 1) *Sex*: All animal subjects were identified as male or female. 2) *Age*: I categorized subjects into three age-classes - young adult, adult and old adult - based on morphological characteristics such as body size, skin and developmental stage of sexual organs (Ilham et al., 2017; Poirier & Smith, 1974). 3) *Rank*: I calculated the dominance ranks of macaques based on their dyadic interactions with clear submissive signaling (such as silent bared teeth, body bending away, and/or running away), which were extracted from the focal sampling data. I then employed David's score (David, 1987), as implemented in the *Elorating* package (Neumann & Kulik, 2020), to compute ordinal ranks of individual animals based on the weighted sum of their direct and indirect wins and losses in dyadic agonistic encounters (De Vries et al., 2006).

Social behavior: From the continuously recorded focal animal sampling data, I calculated 1) *Groom*: the percentage of total observation time spent by each macaque giving or receiving grooming from a conspecific. I also calculated 2) *Agonism,* as the frequency per unit time of the focal individual showing submission (avoidance, silent bared teeth, flee) or receiving

aggression (open mouth stare, brow flash, ear flap, chase, bite, or slap) from other macaques. To estimate 3) *Exposure to humans*, I categorized each individual into three levels based on the frequency of interactions with humans (provisioning-and-feeding, approach-and-avoid, and aggression given or received) observed during the entire observation period, based on the distribution of the behavior sampling data that revealed a bimodal distribution with many individuals showing no interactions with humans (low: zero interaction, medium: 1−2 interactions, and high: more than two interactions).

Stress-related and sickness behavior: I calculated the rates of 1) *Self-scratching* as an indicator of stress (Troisi et al., 1991) from the focal sampling data as the number of times the focal individual was observed scratching themselves, divided by the total observation time. I also calculated 2) *Dominance (un)certainty* as the probability that an individual is certain of its dominance rank given its wins and losses in agonistic encounters. I calculated this measure by extracting an edge list of dyadic agonistic interactions with clear submission during focal follows. I used the *Perc* package in R (R Core Team et al., 2021) to obtain uncertainty values, which range from 0.5 (total uncertainty) to 1 (total certainty) (Fujii et al., 2015). In captive macaques, dominance certainty has previously been strongly linked with biological markers of health and stress, where high-ranked animals with more ambiguous status relationships had higher levels of inflammation than low-ranked animals, whereas little effect of rank was seen for animals with more certain status relationships (Vandeleest et al., 2016). Finally, observers recorded the frequency of 3) *Coughing events* from the behavioral sampling as indicator of potential symptomatic illness and disease (Peña & Ho, 2015).

Biological specimen collection

We collected biological specimens opportunistically using two non-invasive methods for MTBC determination (Figure 1.1). 1) Fecal swab: the freshly dropped feces from identified individuals, which relied on MTBC shedding in sputum, subsequent swallowed by animals, and excreted in feces (Wolf et al., 2016), and 2) Rope bait method: the ropes were used to bait to animals and to collect samples inside their oral cavity, in which a macaque was allowed to chew a rope that was dipped into sweet syrup and ultimately discarded the rope onto the ground when the sweetness was gone (Toyoda et al., 2020). Both fecal specimens and chewed ropes were collected immediately, stored in a lysis buffer (Meesawat, Aiempichitkijkarn, et al., 2023), brought to the laboratory at National Primate Research Center of Thailand-Chulalongkorn University (NPRCT-CU), and analyzed. The nested polymerase chain reaction (PCR) was used to detect a nucleic acid sequence (IS*6110*) unique to MTBC (Detail in Supporting Information). This method has been validated for identifying macaques with active infection of MTBC under conditions of natural exposure (Meesawat, Warit, et al., 2023; Wolf et al., 2016). Detection sensitivity for active infections was estimated at 50% and specificity was 100% (Wolf et al., 2015). The optimized MTBC nested PCR method used in this study is highly sensitive and can detect MTBC during the active shedding stage of infection. The limit of detection values for the first and second rounds of PCR were 100 fg/μL and 10 fg/μL, respectively (Meesawat, Aiempichitkijkarn, et al., 2023)

My research team collected at least four (fecal and rope bait combined) samples per individual, spread across the study period. An animal was indicated as active TB if at least one collected sample showed a positive result, otherwise, it was considered to be TB negative. Since the immune response of monkeys to the MTBC was not determined in this study, the latent stage

was not considered. For the 98 focal individuals, I performed nested PCR in a total of 394 collected specimens; these were obtained from 240 fecal samples (average 2.45 fecal samples/individual), and 154 rope samples (average 1.57 rope samples/individual).

The protocols used for this research were approved by Institutional Animal Care and Use Committee (IACUC) of the UC Davis #22482 and of the NPRCT-CU #2075007. All field data collectors completed chest x-rays to verify negative TB status before entering the field site, and they wore face masks during observation.

Figure 1.1 Biological samples collection: (Left) Monkey defecating. (Right) Monkey chewing a baited rope

Data analysis

All predictor variables were converted to Z-scores to avoid biases in variable importance (Colan, 2013). To assess the effects of demographic and behavioral factors on MTBC detection, I used Generalized Linear Models (GLMs) with a logit (logistic) link function (Wright, 1995), using the *stats* package in R (R Core Team et al., 2021). To identify the most biologically meaningful combination of predictor variables that affected TB, I employed an Information-Theoretical approach (Burnham et al., 2011) and Akaike information criterion (AIC) score as the criterion for model selection (Akaike, 1973).

To this end, I first constructed three distinct models based on different sets of predictor variables: one focusing on macaques' sociodemographic factors (sex, age class, rank), another on social behavior (durations of grooming, rates of agonistic behavior, and levels of human interaction), and the last one on stress-related or sickness behaviors (rate of self-scratching, dominance rank certainty, and frequency of coughing). Within each model, I identified the variables that contributed to the model's ability to fit the observed data. Instead of using a stepwise approach, I evaluated the performance of these three models using the corrected AIC (AICc) score as the criterion for model selection, especially pertinent for small data sets (Bartoń, 2023). The final model set would include the important variables from each of the main models, along with interactions. This method allowed me to compare the relative importance of demographic factors, social behaviors, and stress-related or sickness behaviors in predicting the response variable.

After obtaining the final set of models, I further assessed interactions among the best predictive variables, to explore whether they collectively or combinatorically (as opposed to individually) impacted the likelihood of TB infection. I did so by determining whether the inclusion of specific interaction terms improved the model's performance, both by comparing AICc scores with the best-fit model and by conducting a likelihood ratio test (LRT) to compare the interaction model with the best-fit model. I performed model diagnostics tests on my final model − specifically checking for multicollinearity by measuring variance inflation factors (vif) using the *car* package (Fox & Weisberg, 2019).

Results

Prevalence of TB among long-tailed macaques

PCR-based MTBC detection revealed that out of the 98 individuals on whom I ran these tests, 11 macaques tested positive (11.22%) in either fecal samples (8 animals) or rope samples (3 animals), and were therefore diagnosed as active TB. No animal was detected MTBC in both fecal and rope specimens. All positive animals had one positive result out of four tests (detailed in Supporting Information). I noticed no signs of illness (i.e., coughing, lethargy) among MTBC positive animals compared to non-MTBC detected individuals.

Impact of socio-ecological factors and stress indicators on TB status

Among the three main models I ran (as summarized in Table 1.1), only the model focusing on social behavior (AICc = 67.46) yielded an AICc score lower than the null model (AICc = 70.87). Within the social behavior models, I assessed each variable separately to identify their contribution. The best-fit model included both *Grooming* and *Exposure to humans* as predictors, demonstrating the best fit with an AICc score 6.24 points lower than the AICc score of the full model. Additionally, this model outperformed a model that incorporated an interaction term between grooming and anthropogenic exposure (ΔAICc = 1.40). The result from a likelihood ratio test (LRT) indicated that the difference between the models was not statistically significant. Overall, the best-fit model revealed strong evidence for the *H1 Human Interaction Hypothesis*. Specifically, macaques' exposure to anthropogenic factors, i.e., their frequency of interactions with humans, significantly and positively predicted the likelihood of TB acquisition (Figure 1.2B). Moreover, the model also revealed evidence for the *H3 Sickness-related Hypothesis* – increased grooming of conspecifics was negatively associated with the likelihood of TB acquisition. Finally, I found no support for *H2 Conspecific Interaction*

Hypothesis as I found that engaging in more social interactions does not increase, but indeed decreases the likelihood of individuals' risk of contracting TB (Figure 1.2A). Incorporating *Agonism* into the model raised its AICc value to 67.46, whereas the model excluding it had an AICc of 66.08.

Table 1.1 showed the summary of model statistics and parameter estimates from the null model, the main three models, the selected variables form the best fit main model (Social behavior), and their interaction (outcome: TB presence–absence). Best fit model in bold.

Model	**Variable**	**Estimate**	**Std. error**	**z value**	**p value**	**AICc**
Null	(Intercept)	-2.07	0.32	-6.46	0.000***	70.87
Sociodemographic factors	(Intercept)	-2.71	0.61	-4.44	0.000***	74.97
	Sex (male)	1.35	0.81	1.67	0.095.	
	Age (old)	0.03	0.74	0.04	0.970	
	Age (young)	-15.41	1925.83	-0.01	0.994	
	Rank	-26.04	34.54	-0.75	0.451	
Social behavior	(Intercept)	-0.45	1.25	-0.36	0.722	67.46
	Groom	-6.32	2.90	-2.18	0.029*	
	Agonistic	-0.11	0.11	-1.05	0.295	
	Human (high)	2.79	1.08	2.60	0.009*	
	Human (low)	0.88	0.89	0.99	0.320	
stress-related or sickness behaviors	(Intercept)	9.18	9.01	1.02	0.308	72.19
	Rank certainty	-5.79	7.97	-0.73	0.467	
	Selfscratch	-0.12	0.13	-0.93	0.350	
	Cough	-0.09	0.07	-1.32	0.188	
Groom	(Intercept)	-0.55	0.77	-0.71	0.479	68.55
	Groom	-5.45	2.81	-1.94	0.052	
Agonistic behavior	(Intercept)	-1.88	0.73	-2.57	0.010*	72.75
	Agonistic	-0.02	0.09	-0.27	0.784	
Exposure to humans	(Intercept)	-2.89	0.73	-3.98	0.000***	69.57
	Human (high)	2.08	0.94	2.21	0.027	
	Human (low)	0.76	0.87	0.88	0.379*	
Groom and Exposure to humans	**(Intercept)**	**-1.30**	**0.99**	**-1.32**	**0.186**	**66.06**
	Groom	**-6.06**	**2.84**	**-2.13**	**0.033***	
	Human (high)	**2.44**	**1.00**	**2.44**	**0.015***	
	Human (low)	**0.87**	**0.88**	**0.99**	**0.323**	
Interaction between Groom and Exposure to humans	(Intercept)	-3.15	1.99	-1.58	0.114	67.46
	Groom	0.86	6.04	0.14	0.887	
	Human (high)	6.31	2.90	2.17	0.030	
	Human (low)	2.47	2.28	1.08	0.280	
	Groom:Human (high)	-14.08	9.34	-1.51	0.132	
	Groom:Human (low)	-5.93	7.20	-0.82	0.411	

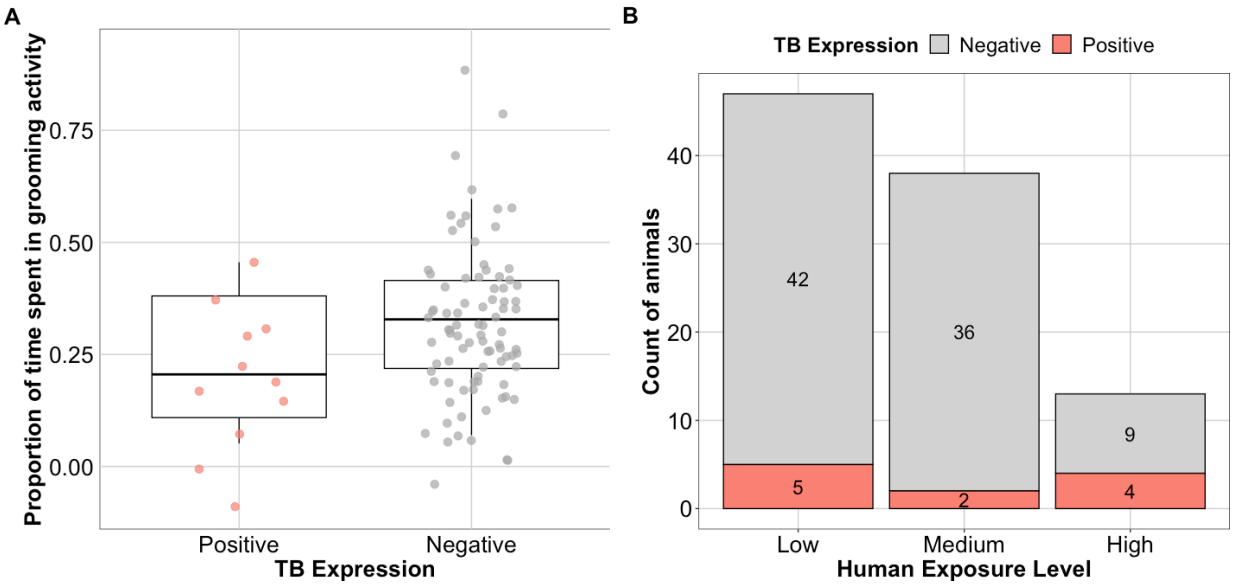

Figure 1.2 A: the boxplot shows that monkeys with TB-positive results exhibited a tendency to spend less time grooming compared to TB-negative monkeys. B: Monkeys were categorized into three human interaction levels (low, medium, and high). Monkeys with high interaction with humans exhibit a significantly higher proportion of positive TB cases compared to those in the low and medium interaction groups.

Discussion

Despite an extensive literature on human systems (Cantwell et al., 1998; Narasimhan et al., 2013b), little is known regarding TB risk factors within free-ranging populations of wild animals due to limited paired data on both infection status and individual behavior on wildlife populations. Nevertheless, these assessments are key to conservation efforts since wildlife may act as natural reservoirs of MTBC, or may themselves be vulnerable to infection and mortality from this (and other) human-borne respiratory pathogens. Wild animals' risk of infection may be driven by numerous factors, including spatial overlap with humans (Wilbur, Engel, & Jones-Engel, 2012), contact patterns resulting from their interactions with conspecifics (Craft, 2015b), as well as inter-individual differences in susceptibility (Cross et al., 2009) .

Among long-tailed macaques in anthropogenic landscapes, here I reveal that inter-individual differences in animals' exposure to anthropogenic factors strongly, positively

influenced the likelihood of TB acquisition, but also that such acquisition may be somewhat offset among individuals that may have experienced a social buffering effect on account of greater durations of time spent grooming their conspecifics.

TB prevalence among macaques and other species

We found eleven out of 98 focal individuals (11.22%) were in an active TB stage, which is consistent with previous sampling (7/72; 9.7%) from the same population using invasive methods (throat swab) in 2020 (Meesawat, Warit, et al., 2023). The same study reported that the TB infection rates in various long-tailed macaque populations ranged from 2.2% to 40%. However, it is noteworthy that the population with the highest TB prevalence of 40% was based on a small sample size of 15 individuals. Generally, many studies focusing on TB in macaques have reported relatively small sample sizes. For instance, Wilbur et al. found that 31.3% of macaques in Thailand were infected with MTBC, which included five out of ten long-tailed macaques, but none among the four *M. arctoides* and two *M. assamensis* tested positive (Wilbur, Engel, Rompis, et al., 2012b). One reason for this could be related to the methodological challenges involved in isolating and characterizing MTBC. For example, this study only tested macaques that had been trapped and brought to the zoo because they had either been injured or were showing signs of respiratory illness. The complexity of diagnosing TB is further exacerbated by the pathogen's ability to have extended and variable benign or latent phases, while the nested PCR method can only detect active TB cases where the pathogen is actively shedding.

Other potential explanations for the observed prevalence levels might be genetic and physiology differences in nature rather than purely methodological. For instance, data from Thailand indicates that the average prevalence of MTBC positive cases is higher in rhesus

macaques (*M. mulatta*; 37%) compared to long-tailed macaques (5.1%) (Meesawat, Warit, et al., 2023). Research on various wildlife populations, particularly deer, has revealed diverse prevalence levels of infection. Specifically, the prevalence of infection has been documented to be as high as 27% in red deer and 18% in fallow deer (*Dama dama*) in Spain (Vicente et al., 2006). These findings collectively emphasize the importance of comprehending the factors that influence prevalence levels among different species. Such understanding can provide valuable insights into broader physiological dynamics and assist in contextualizing the prevalence observed in specific studies.

Impact of anthropogenic exposure on likelihood of MTBC Detection

We found strong evidence for the *H1: Human Interactions Hypothesis*, i.e., for a significant positive relationship between exposure to interactions with humans and the likelihood of MTBC infection. The primary form of human-macaque interaction within the studied group primarily involves food provisioning, with instances of aggression being rare. This pattern closely aligns with previous research indicating that populations engaging in interactions with humans tend to exhibit higher TB prevalence (Wilbur, Engel, & Jones-Engel, 2012). Moreover, instances of disease outbreaks originating from human-to-macaque transmission have been documented in captive settings (Gong et al., 2017; Mätz-Rensing et al., 2015). In my study, I present evidence on wild macaques that frequently overlap and live in dense populations near human settlements. Moreover, I show how inter-individual differences in macaques' exposure to humans are critical in terms of understanding animals' relative vulnerability to acquiring TB.

Therefore, my findings enhance our understanding of the dynamics that drive TB prevalence in wild populations. Such inter-individual differences in anthropogenic exposure may also culminate in more complex patterns of macaques' spatial-social juxtaposition and co-

occurrence with humans and other anthropogenic factors (e.g. livestock, feral mammals) in these areas (Balasubramaniam et al., 2021, 2022). Identifying and quantifying such complexity using network-based tools (Balasubramaniam et al., 2022; Silk et al., 2017; Snijders et al., 2017; Weber et al., 2013) would be a logical next-step towards understanding the dynamics of TB transmission at these (and other) human-wildlife interfaces, which would be of utmost importance for the conservation and management of these urban wildlife populations.

Impact of grooming behavior on likelihood of MTBC detection

According to H2: *Conspecific Interaction Hypothesis*, individuals with more grooming interactions would have higher likelihood to have TB. However, my findings observed an inverse relationship: monkeys less engaged in grooming were more likely to have active TB. This contradicts the expectation that increased socialization would heighten infection risk through contact transmission. Instead, infected individuals are likely to not be involved in grooming activities. The lack of involvement in grooming activity could be related to stress, as individuals who were less likely to engage in grooming exhibited a higher risk of expressive active TB. This finding underscores the potential importance of grooming behavior in enhancing immune defense mechanisms and reducing the risk of infection (Balasubramaniam et al., 2016).

Thus, this instead supported the *H3: Sickness-related Hypothesis*. Specifically, macaques' durations of time spent grooming were negatively associated with the likelihood of TB acquisition. There may be more than one, non-mutually exclusive explanation for this finding. First, affiliation behavior like grooming can socially buffer individuals against disease expression. In humans, for example, stress levels (Janowski et al., 2012) and susceptibility to non-communicable diseases (Uchino, 2009) can be reduced by having more social connections that can offer assistance during times of conflict. Moreover, the progress from the latent TB

stage to the active TB stage can be induced by stress (Dutta & Karakousis, 2014). In primates, grooming is known to lower circulating levels of glucocorticoids by reducing activation of the HPA axis (Young et al., 2014). One study from captive rhesus macaques showed that social stressors led to increased susceptibility to disease in individuals with a personality characterized by low sociability compared with individuals with high sociability (Capitanio, 2011).

Alternatively, the negative relationship between grooming and TB infection could be consequences of the sickness rather than its cause. Specifically, animals may choose, or be forced to reduce their grooming time as a consequence of TB infection and associated sickness and social distancing (Stockmaier et al., 2021). For example, wild mandrills avoid grooming conspecifics infected with orofecally transmitted parasites (Poirotte et al., 2017). Similar patterns have been seen in TB test-positive badgers who socially isolated themselves from their own groups (Weber et al., 2013). Infected individuals might also undergo behavioral or physiological changes leading to decreased social interactions. Symptoms like lethargy or altered grooming behavior can affect their social standing, pushing them to the group's periphery. Similarly, vampire bats with weakened immune systems groom less (Stockmaier et al., 2020), virus-infected bees share less food (Geffre et al., 2020), and humans exposed to bacterial endotoxin feel more socially disconnected, reducing social contacts (Eisenberger et al., 2010).

Further research involving repeated biological and behavioral sampling both pre- and post-infection is important to verify this explanation. By consistently monitoring individuals before and after they contract an infection, we can gain a more comprehensive understanding of the behavioral changes and their correlation with the disease progression. Such rigorous and repeated sampling would provide a clearer picture of the causal relationship between grooming behaviors and TB infection rates.

Agonistic behavior as a potential factor

Previous studies have shown that social disruption can be a risk factor for TB in meerkats (Drewe, 2010a). While I did account for agonistic interactions in my models, it did not show a significant impact comparing to the model without agonistic interactions. A potential reason might be that I overlooked the aspect of directionality in these interactions. Further investigation into the role of agonistic behavior on TB risk should consider the directionality of aggression-submission. For instance, the impact of participation in agonistic behavior may depend on the severity, directionally and chronicity of the aggression experienced, as well as the social context in which it occurs. Given the potential significance of agonistic behavior in understanding the interplay between social and environmental factors that influence immune system functioning and susceptibility to infectious diseases, future studies could delve deeper into this area of investigation.

Limitations and considerations

Our study had important limitations, which would need to be considered and incorporated in future research on these populations. First, I only considered overall rates and durations of animals' direct interactions. In reality, the patterning, distribution and directionality of animals' social interactions with their conspecifics underlie complex social structure, which may influence the likelihood of TB acquisition and transmission. For instance, in the case of meerkats, individuals who engaged more in giving grooming were observed to be more susceptible to TB infection compared to individuals who received grooming. Conversely, while being on the receiving end of aggression correlated with *M. bovis* infection, initiating aggression did not exhibit such an association (Drewe, 2010b).

Over the past 15 years, network analysis has emerged as a pivotal tool in infectious disease epidemiological research (Craft & Caillaud, 2011b). This approach delves into the patterns of interactions among individuals in a population, discerning who interacts with whom, gauging the frequency, and understanding the directionality. By mapping out these interactions, valuable insights are gleaned into the potential mechanisms through which infections may spread or be mitigated in animal populations.

A second limitation of my study is not having evaluated physiological indicators of animals' stress or sickness levels due to logistic constraints. Physiological markers offer a direct and quantifiable insight into an animal's health status and overall well-being. To circumvent this limitation, I employed behavioral indicators, such as self-scratching, dominance uncertainty, and coughing, as proxies for stress and illness. However, my results indicated non-significant findings using these behavioral proxies, underscoring the potential discrepancies between behavioral and physiological indicators. While behavioral cues can provide valuable insights, they might not always align with the underlying physiological realities. Investigating physiological and behavioral responses to infection, such as changes in immune response, stress levels, or social behavior, can help elucidate the underlying mechanisms behind isolation, removal, or social buffering behaviors observed in animals. Future research should prioritize the integration of both behavioral and physiological evaluations to ensure a holistic and accurate understanding of animal health and stress dynamics. It is imperative to obtain authentic physiological indicators, as they can conclusively demonstrate the link between stress and infection susceptibility.

Furthermore, my research utilized a non-invasive testing method that identifies only active TB cases, leaving out latent ones. This decision was in line with my objective to

understand the potential for disease transmission between individuals, as only those with active infections are releasing infectious agents. Exploring non-invasive methods to detect latent TB could be a promising direction for future research. Such an approach would allow for a thorough examination of behavioral patterns and multiple evaluations to distinguish between social buffering and avoidance behaviors effectively.

Processing and screening of TB among wildlife populations has historically presented multifaceted challenges logistically. Since TB is an airborne disease primarily impacting the respiratory system of its hosts, it is imperative to anesthetize the macaques before undertaking invasive procedures like bronchoalveolar lavage or oral-pharyngeal swabs. Such procedures carry risks for both the macaques and the humans involved. To address this challenge, my research adopted non-invasive methods for specimen collection, notably from freshly defecated feces using fecal swabs and from rope-baited buccal cells published previously (Meesawat, Aiempichitkijkarn, et al., 2023). Following collection, I applied the nested-PCR technique to identify the MTBC during the active stage of the disease.

In summary, further research and interdisciplinary approaches combining behavioral ecology with implementing social network analysis and evaluating physiological indicators of animal health and disease would provide more valuable insights into the complex interactions between TB infection status, animal sociality, and health indicators in these populations.

Chapter 2: Social-Network-Based Predictors of Tuberculosis Infection Risk in Long-Tailed Macaques: Unraveling the Complex Interactions between Social Buffering and Contact Transmission

Introduction

Group living and sociality offer significant benefits to animals such as decreased predation risk and increased resource access, but also brings costs such as opportunities for infectious agents to spread through social groups (Altizer et al., 2003; Rifkin et al., 2012; Sandel et al., 2021b). Traditional epidemiology theory predicts that social transmission of infectious agents should increase with group size in animal societies (Altizer et al., 2003; Nunn et al., 2015; Sah et al., 2018a) with supporting data coming from meta-analyses (Patterson & Ruckstuhl, 2013; Rifkin et al., 2012) and as well as empirical studies in hawks (Whiteman & Parker, 2004), ungulates (Ezenwa, 2004) and across primates (Davis & Stamps, 2004; Griffin & Nunn, 2012). Nevertheless, there remain inconsistencies in the correlations between group size and infectious disease outcomes. No relationship has been found in marmots (Arnold & Anja, 1993) and primates (Semple et al., 2002); negative relationship in rodent (Bordes et al., 2007); and positive relationship in horses (Rubenstein & Hohmann, 1989). Such equivocal results indicate that the group size of groups alone is not sufficient to capture the dynamics of disease transmission in social animals (Nunn et al., 2015). It follows that network connectivity should be examined to understand how the infection spreads in a group.

Traditionally, epidemiological models that assess disease transmission through animal social groups have assumed that animals within groups interact randomly (Bansal et al., 2007b). In reality, however, individual animals differ in terms of both the number and the extent to which

they interact with their conspecifics (Craft, 2015b). Social network analysis provides the means to capture such heterogeneity in interactions between individuals (Lazega et al., 1995b). In simple terms, a social network is composed of nodes (individuals) interlinked by edges (interactions), and diseases can spread along edges according to who associates with whom (Bansal et al., 2007b; Rushmore et al., 2014b). During the past two decades in particular, social network analysis has been extensively used as a tool to study how variation in animal-animal spatial and social interactions and emergent social structures might influence the spread of infectious agents through groups (reviewed in Craft & Caillaud, 2011).

One such gap pertains to the contrasting effects of an individual's connectedness (centrality) on disease outcomes. On the one hand, extensive research has assessed and revealed evidence for how direct physical interactions between individuals and therefore their emergent connectedness within social networks may facilitate the contact-mediated transmission of infectious agents. Individuals generally have a higher risk of infection if they are better connected (more central) in the network (Drewe et al., 2011b; Romano et al., 2016b). The high-centrality individuals can act as potential "super-spreaders" who can amplify disease transmission within a network by acting as hubs of transmission and playing a key role in outbreaks (Lloyd-Smith et al., 2005; R. A. Stein, 2011).

On the other hand, in the context of social buffering, centrality within a network does not necessarily increase the risk of disease acquisition but can instead serve as a protective factor. Numerous studies have shown that individuals with high centrality in their social networks often benefit from emotional and instrumental support, which can reduce stress levels (reviewed in Ozbay et al., 2007). Lower stress levels, in turn, are associated with a stronger immune response and reduced vulnerability to infections (Padgett & Glaser, 2003). This perspective posits that an

individual's position in a central network can offer them access to social support, which, in turn, mitigates stress-induced susceptibility to diseases (Nordin, 2015).

The contrast between contact-mediated transmission and the social buffering explanation involves an intricate interplay between network structure and disease dynamics (Sah et al., 2018a). Networks created from empirical observation (Rushmore et al., 2014b; K. L. VanderWaal et al., 2014) have been employed to yield insights regarding the influence of network structure on disease spread in nonhuman animals. Much of this research has focused on either wildlife populations in more natural habitats (Drewe & Perkins, 2015) or in captivity (Balasubramaniam et al., 2016). In contrast, our understanding of wildlife populations in anthropogenically impacted urban and peri-urban environments remains limited (Maréchal et al., 2016). The emergence of zoonotic pathogens, with a particular emphasis on respiratory pathogens, in densely populated urban and peri-urban areas, poses distinctive challenges and risks, thereby emphasizing the imperative for a redirection of research focus (Lindahl & Magnusson, 2020).

Our study assessed the potentially competing roles of contact-mediated transmission and social buffering on the risk of infection from respiratory transmission, TB on a free-ranging group of long-tailed macaques. For this project, I proposed the following question based on exploratory research to shed light on the mitigation of disease outbreaks in wild primate populations: contact-transmission or social buffering—what role does the social network position of individual macaques play in their infection status, and in which type of network does this role become most evident?

Contact-transmission versus social buffering

Individuals who are more central or well-connected within their social networks would have a higher probability to be infected by TB (Drewe, 2010b), as they have a higher probability of contacting infected individuals and acquiring infectious agents. *H1: contact-mediated transmission hypothesis* predicts that individuals with high centrality in prosocial networks are more likely to be tested positive for TB, relative to individuals with low centrality.

In contrast, according to the *H2: social buffering hypothesis*, individuals with more social connections reap stress-alleviating benefits that make them socially buffered and less susceptible to infection (Balasubramaniam et al., 2016). Moreover, post-infection changes to the behavior of individual animals to reduce their social connectedness (disease coping strategies like passive or active self-isolation, avoidance, or exclusion (Poirotte et al., 2017; Rushmore et al., 2013; Silk et al., 2019)) may also explain the observed negative relationship between network centrality and the likelihood of TB infection. In accordance with the social buffering hypothesis and/or the disease-coping hypothesis, I predicted that macaques who were more peripheral (rather than central) in their grooming and/or proximity networks, and/or still more central (rather than peripheral) within their aggression networks, would be the most likely to be infected by TB.

Importantly, contact-mediated transmission hypothesis and social buffering hypothesis are not mutually exclusive; they recognize that various situations can arise where social buffering may override contact transmission or vice versa (Balasubramaniam et al., 2016). The interplay between these hypotheses is complex and depends on the specific circumstances of the disease, the network structure, and other contextual factors. Exploring the nuances of how these hypotheses interact in different scenarios is a fundamental aspect of understanding disease dynamics in social networks.

Materials and Methods

Study site and subjects

The fieldwork was conducted at WKT in Petchaburi Province, Thailand (13° 02' N, 99° 57' E). The study population consisted of macaques divided into three separate groups totaling around 400 individuals (Aiempichitkijkarn et al., unpublished data). The primary focus was on the largest group, which mainly inhabited the main temple areas, and within this group, 149 adult macaques were identified. Between the years 2021 and 2022, both focal behavioral data and biological samples were collected from 101 macaques within this study population. However, during the data collection process, three individuals had to be excluded from the analysis due to a lack of sufficient behavioral data, bringing the final sample size to 98 animals for evaluation.

At least four biological samples (feces or orally baited rope) per individual were tested for the presence of the MTBC. The detection involved identifying a specific nucleic acid sequence, *IS6110*, using the nested PCR method. The nested PCR method was employed due to its sensitivity in identifying the IS6110 sequence within the MTBC (Meesawat, Aiempichitkijkarn, et al., 2023). An animal was designated as having active TB if at least one of its collected biological samples tested positive for this sequence; otherwise, it was categorized as TB negative. Among these animals, 11 individuals tested positive, representing an infection rate of 11.22%. For detailed information regarding the TB diagnostic methods employed in this study can be found in Supplementary Material.

Data collection and network measures

We conducted focal sampling (Altmann, 1974) to observe social behavior of 98 macaques. Each animal was observed for a period of ten minutes per day, following a pre-

determined pseudo-randomized order. During each focal session, my research team recorded in a continuous manner social interactions involving the focal animal, and its conspecifics, specifically instances of agonistic interactions (such as threat displays, chasing, silent bared teeth, body bending away, and/or running away), durations of time spent allogrooming, and instances of mounting. Furthermore, we also paused continuous data collection once every two minutes, to conduct an instantaneous scan sample (as in Kaburu et al. (2019)). In these scans, we recorded the focal animal's main activity (i.e., whether subject was interacting with humans, interacting with conspecific, eating anthropogenic food, eating natural food, locomoting, or resting), the density levels of conspecific (i.e., low: 0-11 monkeys, medium 11-20 monkeys, high: more than 20 monkeys) within 20 meters of the focal animal. Additionally, we recorded the presence of dogs, humans, and identity of the conspecifics that were within the body length of the focal monkey. At the end of the data collection period, we collected 1,230 hours of focal data in total, with a mean of 753 minutes per individual focal animal. More details regarding the data collection methods used may be found in Chapter One.

To investigate the effect of individuals' social connectedness on the likelihood of TB infection, I constructed social networks based on macaques' (i) grooming (proportion of total observation time spent giving and receiving grooming), (ii) agonistic interactions (all instances of aggression or submissive responses initiated by either party), and (iii) social proximity (macaques within a body-length of each other, extracted from the point-time scans) with conspecifics. My choices stemmed from the biological relevance of these behaviors and emergent network connectedness for infectious disease risk (see Introduction). First, grooming networks are well-documented for the benefits of being socially buffered against infection

(Balasubramaniam et al., 2016) and the costs of putting individuals at greater risk or susceptibility for acquiring enteric pathogens via contact-mediated transmission (Drewe, 2010b).

In contrast, agonistic interactions, such as aggression and submissive responses, can be indicative of social stress and disruption within a group. For instance, research on meerkats (*Suricata suricatta*) revealed that individuals on the receiving end of aggression were significantly more likely to be infected with *M. bovis* (Drewe, 2010b). Lastly, the finding that TB test-positive badgers (*Meles meles*) were socially isolated in proximity networks highlights the significance of studying proximity networks in understanding disease dynamics (Weber et al., 2013).

All networks were constructed using weighted data (that is, I considered the proportion of time spent grooming, the rate of agonistic interactions, and the number of times two individuals were in proximity, rather than simply recording the presence or absence of an interaction). The grooming network and the agonistic network were extracted from the focal observation and were treated as directed networks (separate between giving and receiving), while the proximity network was extracted from the point-time scan and was treated as an undirected network. All data were weighted by the total observation time of the initiator and individual recipients to account for inter-individual differences in observation durations.

Network centrality

Measurements of network centrality have been used as an indicator of the strength and distribution of social relationships and thus potentially their ability to spread disease (Drewe, 2010b; Romano et al., 2016b). The *igraph* package (Csardi & Nepusz, 2006) in R was used to compute the following centrality measures 1) Degree centrality (number of an individual's direct connections), 2) Strength centrality (number and strength of an individual's direct connections)

3) Eigenvector centrality (the strength of an animal's direct connections and the strength of connections held by that animal's neighbors) 4) Betweenness centrality (the number of pairwise shortest paths in which a given node is present). To visualize the network graphs in my study, I employed the *qgraph* package (Epskamp et al., 2012) in R and implemented the Fruchterman-Reingold algorithm for layout (Fruchterman & Reingold, 1991). This algorithm, a force-directed layout technique, positions nodes with higher degrees of centrality, indicative of more connections, closer to the center of the layout, while nodes with fewer connections are pushed towards the periphery. This approach allowed me to visualize and analyze the complex relationships within the networks.

Data analysis

To assess the effects of demographic and behavioral factors on TB infection, I used Generalized Linear Models (GLMs) with a logit (logistic) link function (Wright, 1995), using the *stats* package in R (R Core Team et al., 2021). To identify the most biologically meaningful combination of predictor variables that affected TB, I employed an Information-Theoretical approach (Burnham et al., 2011) to build models for each centrality measure in the social networks. I used these models to investigate the effect of social network metrics and their interactions on TB infection in individual macaques.

To account for potential issues like collinearity, I avoided including centrality measures from the same network in the same model. To select the most suitable models, I performed univariate models for each centrality measure in each network. The model with the lowest Akaike information criterion (AIC) score (Akaike, 1973) for each network was chosen as the best predictor. Then, I specifically examined the effect of interaction between the grooming network and the agonistic network by combining the best predictive centrality measure from

each model. I did not include combinations of the centrality measure from the proximity network with those of other networks (grooming and agonistic networks) as they are not fully independent. I then checked whether the inclusion of specific interaction terms improved the model's performance, both by comparing AICc scores with the best-fit model and by conducting a likelihood ratio test (LRT) to compare the interaction model with the best-fit model. I performed model diagnostics tests on my final model − specifically checking for multicollinearity by measuring variance inflation factors (vif) using the *car* package (Fox & Weisberg, 2019). This approach allowed me to identify the most informative predictors within each network, while also shedding light on the relationship between social networks and TB infection.

Results

Network centrality and TB infection

a. Grooming Network: Grooming centralities consistently exhibited a negative relationship with TB infection (detailed in Table 2.1). Specifically, groom indegree emerged as the best-predicted variable within the grooming network, as indicated by its lowest AICc score, followed by groom eigenvector and groom instrength, respectively. Importantly, all three centrality measures showed negative trends in predicting TB infection (p values < 0.1). Figure 2.1a represents the grooming network. Notably, the figure highlights that individuals infected with TB tend to occupy peripheral positions within the network, while uninfected individuals are more centrally located.

b. Agonistic Network: In contrast to the grooming network, my analysis of agonistic network centrality revealed a more inconsistent relationship among the variables. None of the examined variables within the agonistic network exhibited statistically significant effects, as all

displayed *p* values exceeding 0.1. Among these variables, agonistic instrength emerged as the best predictive variable based on AICc score. However, it is important to note that the differences in AICc values among the examined variables were within two units of each other, suggesting a comparable model fit for each variable. Figure 2.1b provides a visual representation of the agonistic network. Interestingly, the figure does not reveal any discernible patterns or trends that would suggest a clear association between agonistic interactions and TB infection.

c. Proximity Network: Similar to the agonistic network, my analysis of centrality measures calculated from the proximity network also revealed a pattern of inconsistency and a lack of statistically significant effects among the variables. None of the examined variables within the proximity network displayed statistical significance, as all yielded *p* values above 0.1. Figure 2.1c provides a visual representation of the proximity network. This figure does not reveal any noticeable patterns or trends that would suggest a clear association between proximity-based interactions and TB infection.

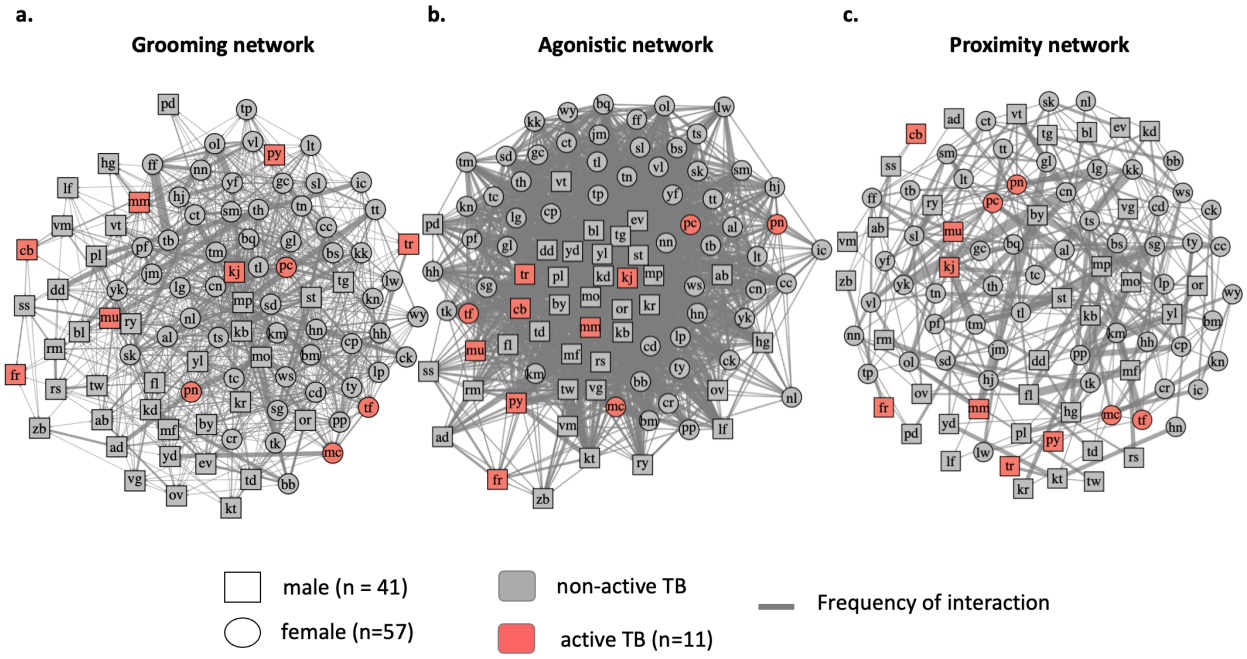

Figure 2.1 Social Network Structures provides a visual representation of the social network structures of 98 focal individuals within the study group. In the figure, square symbols denote male individuals, while circular symbols represent females. Individuals with active TB status are highlighted in red. The thickness of the lines connecting individuals signifies the intensity of interaction. (a) illustrates the grooming network, constructed from grooming duration in dyadic interactions. (b) depicts the agonistic network, based on the frequency of aggressive and/or submissive behaviors. (c) showcases the proximity network, relying on the proximity of individuals within a body length during scan samples. These visualizations offer insights into the social dynamics and associations between individuals in the context of the study.

Table 2.1 showed the univariate models from each network type (outcome: TB presence–absence). The models with AICc lower than that of the null model are indicated in bold.

Network	Predictor	β	Std. Error	*p* value	AICc
Null	(Intercept)	-2.07	0.32	0.000***	70.87
a) Grooming network	**(Intercept)**	**-0.59**	**0.75**	**0.434**	**68.71**
	Groom indegree	**-0.12**	**0.06**	**0.053.**	
	(Intercept)	**-1.11**	**0.55**	**0.044***	**68.95**
	Groom eigenvector	**-4.22**	**2.41**	**0.080.**	
	(Intercept)	**-0.89**	**0.69**	**0.197**	**69.36**
	Groom instrength	**-21.14**	**12.47**	**0.090.**	
	(Intercept)	-1.30	0.62	0.037*	71.09
	Groom outdegree	-0.06	0.05	0.195	
	(Intercept)	-1.79	0.41	0.000***	71.85
	Groom betweenness	-11.05	11.99	0.357	
	(Intercept)	-1.67	0.54	0.002**	72.19
	Groom outstrength	-6.67	8.03	0.406	
b) Agonistic network	(Intercept)	-2.14	0.34	0.000***	71.31
	Agonistic instrength	-0.43	0.34	0.211	
	(Intercept)	-2.11	0.33	0.000***	71.98
	Agonistic indegree	-0.32	0.33	0.330	
	(Intercept)	-2.08	0.32	0.000***	72.55
	Agonistic betweenness	0.18	0.27	0.503	
	(Intercept)	-2.07	0.32	0.000***	72.81
	Agonistic eigenvector	-0.13	0.34	0.702	
	(Intercept)	-2.07	0.32	0.000***	72.90
	Agonistic outdegree	0.07	0.31	0.812	
	(Intercept)	-2.07	0.32	0.000***	72.96
	Agonistic outstrength	0.01	0.32	0.972	
c) Proximity network	(Intercept)	-2.13	0.34	0.000***	71.76
	Proximity eigenvector	-0.43	0.44	0.328	
	(Intercept)	-2.09	0.33	0.000***	72.52
	Proximity degree	-0.22	0.34	0.519	
	(Intercept)	-2.08	0.32	0.000***	72.71
	Proximity strength	-0.17	0.35	0.630	
	(Intercept)	-2.07	0.32	0.000***	72.89
	Proximity betweenness	0.08	0.31	0.790	

We explored the combination of different centrality measures to enhance the predictive power of my models. Groom indegree was chosen based on the lowest AICc. For agonistic network, all variable's AICs are worse than the AICs of null model. So, I chose agonistic indegree for the ease of interpretation. I assessed models incorporating groom indegree, agonistic indegree, and their interaction (see Table 2.2). The likelihood ratio test revealed that the model including the interaction term performed better than the model without interaction term (*p* value = 0.043).

Therefore, the model that yielded the best results incorporated the interaction between groom indegree (the number of individuals that groom the focal animal) and agonistic indegree (the number of individuals that target the focal animal with aggression, or that the focal animal shows submissive behavior towards). This model demonstrated a significant interaction term with a p-value of 0.0458 and an AIC value of 68.076. These findings suggest that the combined influence of agonistic interactions and grooming behavior plays a crucial role in predicting TB infection risk (Figure 2.2).

Table 2.2 The models with the groom indegree, agonistic indegree, and the interaction

Predictor(s)	**Estimate**	**Std. Error**	**Pr(>|z|)**	**AICc**
(Intercept)	-0.27	0.93	0.773	70.24
Groom indegree	-0.11	0.07	0.079.	
Agonistic indegree	-0.02	0.04	0.560	
(Intercept)	3.01	1.95	0.122	68.16
Groom indegree	-0.40	0.17	0.017*	
Agonistic indegree	-0.23	0.12	0.053.	
Groom indegree : Agonistic indegree	0.02	0.01	0.049*	

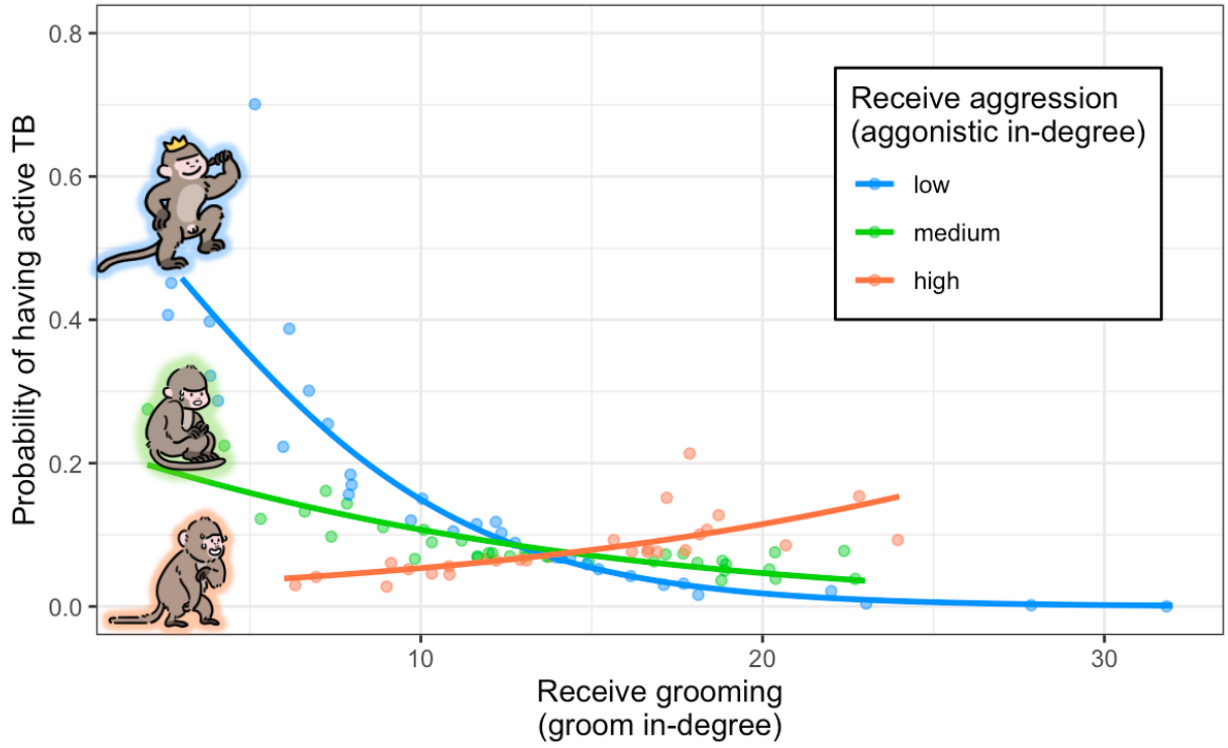

Figure 2.2 Interaction model of agonistic indegree and grooming indegree with probability of active TB. The figure displays the relationship between agonistic indegree and grooming indegree, and their interaction, in relation to the probability of having active TB in macaques. Data points are color-coded to represent different levels of being at the receiving end of agonistic behavior, with blue dots indicating receiving low aggression, green dots indicating receiving medium aggression, and red dots indicating receiving high aggression. The figure provides a visual representation of how the probability of active TB varies based on the interaction between grooming and agonistic behaviors, highlighting the potential influence of submission behavior on TB infection risk in macaques.

Discussion

Grooming network is more important to predict TB infection than agonistic network and proximity network. Grooming centrality consistently shows negative association with TB infection outcomes. These findings support the general trend that an increase in grooming centrality decreases the likelihood of having TB. Specifically, groom indegree (the number of individuals that groom the focal animal) is the most predictive variable. The results suggest that macaques located at the periphery of the grooming network are more likely to exhibit TB

infection, while those receiving grooming from a larger number of individuals (high grooming indegree) have a lower risk of TB infection compared to those receiving grooming from fewer individuals (low grooming indegree).

While agonistic centralities alone do not appear to be significant predictors of TB infection risk, it is intriguing that the interaction between agonistic indegree and grooming indegree yields statistical significance. This suggests that the combined influence of agonistic interactions and grooming behavior plays a unique and important role in predicting TB infection risk within this social network. This finding underscores the complexity of disease transmission dynamics within a primate population and highlights the interplay between social behaviors.

In contrast, proximity centralities did not show as a significant predictor in the model. This may be because the inclusion of grooming centrality and agonistic centrality in the models already accounts for the influence of proximity, as these measures capture aspects of social interactions and relationships closely related to proximity.

Overall, my results align with the *H2 social buffering hypothesis*, which states that individuals with more social connections attain stress-alleviation benefits that make them socially buffered and less susceptible to infection, despite having more opportunities for exposure through their greater number of social interactions. This pattern has been seen in rhesus macaques, where monkeys with more grooming and huddling connections were less susceptible to Shigella infection (Balasubramaniam et al., 2016) and in badgers, where TB test-positive badgers were socially isolated from their own groups (Weber et al., 2013). This study demonstrates the potential health benefits of increased group interactions as a mitigating factor against TB infection in macaques.

The best model incorporating the interaction term reveals intriguing patterns (see Figure 2.2). It illustrates that individuals who receive low to medium levels of aggression, they conform to the general negative trends in line with the social buffering hypothesis. In this scenario, individuals who have lower grooming partners are more likely to contract TB, aligning with the idea that social support via grooming connections can serve as a protective factor.

Conversely, a different trend emerges among macaques experiencing higher levels of agonistic interactions (those often on the receiving end of aggression). These individuals who are experiencing agonistic behaviors from many individuals are more likely to exhibit infection even when engaging in frequent grooming activities. In essence, the influence of social buffering, facilitated by grooming connections, is diminished (if not entirely absent) in individuals subjected to receipt of high rates of aggression. In effect, the receipt of high aggression overwhelms the social buffering effect of grooming putting such individuals in a more susceptible position. This nuanced interplay underscores the complexity of disease dynamics within this primate population, suggesting that the interplay between social behaviors and their influence on infection risk is context-dependent and varies across individuals with different social roles and experiences.

Infected individuals at the edge of grooming network

The main results do not conform to expectations that overall high socialization would lead to high chance of infection through contact transmission. In contrast, infected individuals are likely to be found at the periphery of the group. Certain explanations may account for the presence of infections in individuals who receive less grooming (Stockmaier et al., 2021), as elaborated upon below.

First, other monkeys may avoid contact with infected individuals as a behavioral response to infection. Selection should favor susceptible individuals who can detect and subsequently avoid potentially infectious conspecifics. For example, wild mandrills avoid grooming conspecifics infected with orofecally transmitted parasites (Poirotte et al., 2017). Thus, sick individuals should experience exclusion by other group members and/or receive less social interaction from other group members. This social avoidance should rely on cues that differentiate potentially infectious individuals from healthy group members. However, in my population of macaques, I noticed no increase in aggression and signs of illness for TB (coughing and lethargy) among MTBC detected animals comparing to non-detected individuals.

Second, infectious animals may actively remove themselves from others through behaviors such as social distancing, isolation, or avoidance. This can include avoiding direct contact with other animals, retreating to secluded areas, or reducing social interactions. Similar patterns have been seen in TB test-positive badgers who socially isolated themselves from their own groups (Weber et al., 2013). In humans, this behavior may be a voluntary response to their own infection, as they instinctively recognize that their condition poses a potential risk to others. By actively removing themselves from contact with healthy individuals, infected individuals may reduce the likelihood of transmitting the infection to their peers, thus demonstrating a self-protective mechanism to limit the spread of disease within their social group (McGrail et al., 2020).

Another explanation is that infected individuals may experience changes in their behavior or physiology that result in reduced social interactions. For example, individuals that are infected may exhibit symptoms such as lethargy, weakness, or altered grooming behavior, which could lead to altered social interactions. As a result, infected individuals may be displaced to the

periphery of the group as they may no longer be able to maintain their usual social positions or affiliative interactions with healthy group members. For example, vampire bats that have weakened immune systems groom their fellow bats less frequently (Stockmaier et al., 2020), bees infected with viruses share less food with their nestmates (Geffre et al., 2020), and humans exposed to bacterial endotoxin may report feeling socially disconnected, leading to a decrease in social contacts (Eisenberger et al., 2010).

Lastly, affiliation behavior like grooming can socially buffer individuals against disease expression. Indeed, social buffering appears to be the main operating process underlying TB infection patterns in this population of macaques with the caveat that it can be interrupted by other stress-inducing behaviors such as high rates of received aggression. This is perhaps not surprising as the progression from the latent TB stage to the active TB stage can be induced by stress (Dutta & Karakousis, 2014). In humans and other primates, stress levels (Janowski et al., 2012) and susceptibility to non-communicable diseases (Uchino, 2009) can be reduced by having more social connections that can offer assistance during times of conflict. Socio-positive interactions appear to be key in alleviating stress, which both enhances immune function (Sapolsky et al., 2000) and decreases susceptibility to infectious agents (Cohen et al., 2007; Segerstrom & Miller, 2004). For example, in primates, grooming is known to lower circulating levels of glucocorticoids by reducing activation of the HPA axis (Young et al., 2014). A study on captive rhesus macaques showed that social stressors led to increased susceptibility to disease in individuals with a personality characterized by low sociability compared with individuals with high sociability (Capitanio, 2011). Broadly, these findings add novelty to epidemiological studies implementing social networks by providing evidence for both the costs and the benefits of social connectedness.

Limitation and future directions

Isolation, removal, and social buffering are intertwined factors that can be challenging to disentangle when studying infections in animals. A key limitation of our study is the constraint posed by non-invasive diagnostic tests for TB, which allowed me to detect macaques only in the active TB stage. This limitation makes it nearly impossible to pinpoint the exact timing of infection, especially during the early stages of the disease (de la Rua-Domenech et al., 2006).

Regular testing for infections can enhance early detection, enabling the identification of the initial day of infection. To gain a deeper understanding of disease dynamics within communities, conducting comparative analyses between individuals' or communities' social network positions before and after infection is crucial. Such comparisons can provide invaluable insights into the intricate interplay between disease dynamics and social behaviors.

Furthermore, among laboratory-infected macaques, variations in susceptibility and disease progression are evident (Capuano et al., 2003b), indicating that intrinsic factors, such as stress, inflammatory indicators, and immunity level, would prove valuable in enhancing our understanding of disease dynamics (Dijkman et al., 2019).

Moreover, the inclusion of other tests like the QuantiFERON blood test to detect latent TB could provide valuable insights into the spread of infection (Warit et al., 2020b). However, those tests are highly invasive and difficult to perform in the field. Instead, I propose implementing a Susceptible-Exposed-Infectious-Recovered- Susceptible (SEIRS) model on the observed social network to hypothetically track changes to individuals' disease states and provide modeled situations that can explain how disease spreads through the network (Bjørnstad et al., 2020).

Within the past decade, network compartmental modeling such as SEIRS has been used in wildlife systems and provided basic information of disease transmission that would otherwise be difficult to explore. For example, grooming was more likely than aggression to be correlated with *M. bovis* transmission in meerkats (Drewe et al., 2011b). Targeting the most central chimpanzees in vaccination simulations reduced the number of vaccines needed to prevent an outbreak compared to random vaccinations (Rushmore et al., 2014b). More central individuals transmit infections in a shorter amount of time and to more subjects but also become infected more quickly than less central individuals (Romano et al., 2016b). Incorporating network compartmental modeling techniques like SEIRS into my research not only offers a non-invasive alternative to understand disease spread but also underscores the growing significance of interdisciplinary approaches in unraveling the complexities of infectious disease dynamics in wildlife populations.

Chapter 3: A Susceptible Exposed Infected Recovered Susceptible (SEIRS) Model for the Transmission of Tuberculosis in Long-Tailed Macaques

Introduction

The COVID-19 pandemic has underscored the potential for diseases originating in animals to rapidly escalate into global health crises. Understanding disease transmission among animals is of paramount importance; however, clear scientific knowledge in this domain often remains elusive (Cross et al., 2004; Maréchal et al., 2011a). This dearth of scientific understanding poses significant challenges in controlling diseases and affects both domestic animals and wildlife, thereby endangering human health, animal welfare, and biodiversity. A notable example is the emergence of a new COVID-19 strain among individuals connected to a mink farm in Denmark. Authorities had to resort to the drastic measure of culling over 17 million minks due uncertainty surrounding animal contact patterns and to prevent the emergence of additional novel strains (Frutos & Devaux, 2020). To mitigate such extreme actions and enhance our management of public health risks, a deeper understanding of animal contact patterns and disease transmission dynamics among animals is essential, holding the potential to safeguard human health, animal populations, and environmental preservation.

Understanding and managing diseases in animal populations is challenging due to several factors: the scarcity of information regarding their contact patterns, limitations in the tools available for collecting data on network structure, practical difficulties in detecting diseases in the field, and the availability of potential control options. Each of these elements presents its own set of complications, making the comprehensive management of diseases within animal populations a complex challenge (Craft & Caillaud, 2011b). Researchers have employed

mathematical modeling as a tool to gain insights into disease transmission patterns and potential outcomes (Rushmore et al., 2014b). A very appealing property of models is their ability to easily depict the complexity of the real world, including the challenges listed above. This approach's flexibility allows it to address emerging questions and enhance disease control efforts (Keeling & Eames, 2005; Wei et al., 2022).

While mathematical models have played a crucial role in elucidating disease trends and dynamics, they often struggle to address the uncertainties inherent in real-world datasets (Sorzano, 2021). These uncertainties can stem from various sources, including variations in contact rates, surveillance techniques, and reporting biases (K. VanderWaal et al., 2017). One promising avenue for mitigating these limitations and enhancing the precision of disease modeling, particularly in animal populations, is the incorporation of real-world network data on animal-animal spatial or social interactions, and emergent social network structure (Drewe et al., 2011b; Rushmore et al., 2013; Sandel et al., 2020). By leveraging real-world data on animal contact patterns and social structures, more realistic and context-specific models can be developed. This approach allows me to capture the inherent complexities of animal interactions and provides a deeper understanding of disease dynamics within populations.

The traditional SIR (Susceptible-Infectious-Removed) compartmental model has served as a fundamental tool in epidemiology for comprehending the dynamics of disease transmission (Kermack & McKendrick, 1991; Sah et al., 2018a; Tolles & Luong, 2020). Within this model, individuals undergo a sequence of three states: susceptibility to the disease, infectiousness for transmitting the disease, and subsequent removal or recovery. Nonetheless, the conventional SIR model is simplistic and unable to capture the true complexity of some diseases. For instance, it neither considers or incorporates latent periods, nor does it account for the potential of

reinfection after recovery, a crucial factor in many diseases such as COVID-19 (Cooper et al., 2020). To address these complexities, more sophisticated models like SEIRS (Susceptible-Exposed-Infectious-Removed-Susceptible) have been developed (Bjørnstad et al., 2020).

In particular, SEIRS models are useful to understand the dynamics of respiratory infectious diseases such as TB in wildlife and humans, wherein pathogens can persist among hosts through prolonged and sometimes unpredictable latent phases, as well as have a probability of reinfection (Zong et al., 2018). Despite the World Health Organization's (WHO) ambitious strategic plan to eradicate TB from the world by 2030, continues to pose a significant global health challenge (World Health Organization, 2022). TB's endemic status in numerous countries further complicates efforts to combat this infectious disease (Issarow et al., 2018). Its capacity to remain latent for extended periods also complicates efforts to eradicate this disease (Boom et al., 2021). Furthermore, individual variations in transmissibility and latency periods, influenced by factors such as stress, isolation, and co-infection, add complexity to efforts combatting TB (Capuano et al., 2003b; Hayward et al., 2022; Mehra et al., 2011). To gain a deeper understanding of TB's dynamics, I utilized models like SEIRS with adaptations to account for individual characteristics. This approach allowed for an exploration of who is most susceptible to infection.

Here I delve into the use of compartmental modeling to address these challenges and propose a novel approach that incorporates network data from observations and infectious disease sampling of free-ranging primates to enhance the accuracy and uncertainty estimation in disease modeling. I utilized a dataset from a group of long-tailed macaques, where behavioral observations and infectious prevalence have been systematically recorded, providing a representation of natural TB infection dynamics. A prior study revealed an interesting discovery,

indicating that macaques situated at the periphery of the social network exhibit a higher prevalence of TB (Aiempichitkijkarn et al., unpublished data). This chapter leverages this information, with a specific focus on individual variations in grooming behavior as a potential protective factor against infection. In this study, I have developed models that incorporate diverse transmissibility and latency periods, offering a more realistic representation of individual differences in TB. Through the application of these models, my aim is to shed light on the enigma of disease endemicity and the intricate buffering effect of TB within complex social networks.

Materials and Methods

Study site and subjects

Data and samples were collected on one group of free-ranging long-tailed macaques at WKT in Petchaburi Province, Thailand (13° 02' N, 99° 57' E). Between the years 2021 and 2022, both behavioral data and biological samples were collected from 101 macaques within this study population. However, during the data collection process, three individuals had to be excluded from the analysis due to a lack of sufficient behavioral data, bringing the final sample size to 98 animals for evaluation. 11 of 98 individuals (11.22%) were tested as positive using nested PCR due to its sensitivity for IS*6110* detection within MTBC (Meesawat, Aiempichitkijkarn, et al., 2023). For detailed information regarding the TB diagnostic methods employed in this study can be found in Chapter One.

Behavioral and data collection

I employed the focal sampling method (Altmann, 1974) to investigate the social behaviors of 98 macaques. Each macaque underwent ten minutes of daily observation, following a predetermined, pseudo-randomized sequence, totaling an average of 12.5 hours per individual

(ranging from 10.2 to 14.4 hours). In this chapter, my primary emphasis is on 'groom indegree centrality', representing the number of macaques grooming a specific individual. The result from previous work revealed an inverse correlation between groom indegree and the risk of TB contraction, implying that grooming may offer a protective effect against infection.

I utilized the point-time scan methodology for behavioral data collection during each 10-minute focal observation session. My data collection team temporarily paused continuous data recording every two minutes to conduct six point-time scans (Kaburu et al., 2019), identifying conspecifics within a body length of the focal monkey. After accounting the total scan samplings, I constructed the proximity network using the *igraph* package (Csardi & Nepusz, 2006). This proximity network, which illustrates the frequency at which two animals were observed within a body length of each other, indicates potential avenues for disease transmission. Detailed overview of other behaviors and my methodology can be found in Chapter One.

Baseline transmission model

I developed an individual-level stochastic network model using empirical proximity network data from 98 focal individuals in a long-tailed macaque group. I utilized an extended version of the classic compartmental SIR model (Kermack & McKendrick, 1991), a widely recognized model for tracking disease spread (Tolles & Luong, 2020). Given the characteristics of TB, I adopted the SEIRS model, which introduces a latent period (Exposed) and allows for re-infection after immunity loss (Susceptibility, after Recovery) (Bjørnstad et al., 2020).

This compartmental approach categorizes individuals into specific groups according to their current infection status: S for those susceptible to the disease, E for those exposed (indicating latent TB infection), I for those actively infectious, and R for those who have recovered from TB. SEIRS models can provide hypothetical situations that can explain how

disease spreads through social networks by tracking changes to individuals' disease states at a given time.

We describe the dynamics of TB infection using Ordinary Differential Equations (ODEs). These equations capture the progression by considering both the number of individuals in the previous step and the potential for transitioning between compartments (Bjørnstad et al., 2020).

$$\frac{dS}{dt} = -0.6\,\beta SE - 0.4\,\beta SI + \xi R$$

$$\frac{dE}{dt} = 0.6\,\beta SE - \sigma E$$

$$\frac{dI}{dt} = 0.4\,\beta SI + \sigma E - \gamma I$$

$$\frac{dR}{dt} = \gamma I - \xi R$$

The terms $\frac{dS}{dt}$, $\frac{dE}{dt}$, $\frac{dI}{dt}$, and $\frac{dR}{dt}$ represent the rates of change over time for the Susceptible, Exposed, Infectious, and Recovered compartments, respectively. The equations demonstrate the dynamics between these compartments over time, underpinned by parameters representing the infection potential (β), progression from exposure to infectiousness (σ), recovery rate (γ), and loss of immunity rate (ξ). The model parameters and their explanations can be found in Table 3.1.

Table 3.1 provides definitions for coefficients and population compartments

α	The contact rate, which is the number of infected neighbor(s) in the network with whom an individual comes into contact
β	The overall infection potential, which takes into account the contact rate (α) and the transmissibility rate (τ) per contact, is given by the formula: $\beta = 1 - (1 - \tau)^{\alpha}$
γ	The recovery rate, which is the rate at which infected individuals recover from the disease.
σ	The progression rate, which is the rate at which infected individuals progress from the latent stage to the active stage.
ξ	The reinfection rate, which is the rate at which recovered individuals become susceptible to the disease again.
τ	The transmissibility rate, which is a measure of how easily the disease can be transmitted from one individual to another.

S	The number of individuals in susceptible state
E	The number of individuals in exposed state
I	The number of individuals in infectious state
R	The number of individuals in recovered state

We initiate the simulation by randomly assigning a single infected individual into the network. My simulation progresses in discrete time steps to estimate the probabilities of transitioning between compartments in the contact network. At each time step, I calculate the infection potential (β) for each individual. This is determined by their interactions within the proximity network, represented by α (the number of infected neighbors), and the disease's transmissibility (τ). The relationship is given by the formula: $\beta = 1 - (1 - \tau)^{\alpha}$ (Bjørnstad, 2018).

For long-tailed macaques, 40% of individuals become infected directly (S → I), while the others 60% enter an exposed state (S → E) before transitioning to an infectious state (Capuano et al., 2003b). Then, I account for individuals moving from the exposed state to the infectious state (E → I), those recovering (I → R), and those becoming susceptible again (R → S). The population in each compartment (S, E, I, R) is updated accordingly (Figure 3.1). In order to explore the connection between groom indegree and the probability of infection, I employed three distinct models: the Baseline Transmission Model, the Individualized Transmissibility Model, and the Individualized Latency Model.

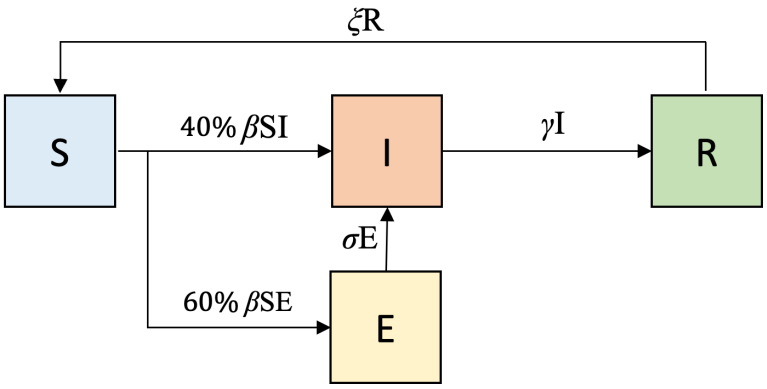

Figure 3.1 The SEIRS model flow chart depicts transitions through different states. In this model, 60% of susceptible individuals move to the Exposed state at a rate of βSE, while the remaining 40% directly transition to the Infected state upon exposure at a rate of βSI. Following a latent period, exposed individuals transition to the Infectious state at a rate of σE. Infected individuals recover at a rate of γI, transitioning to the Recovered state. Over time, recovered individuals lose immunity at a rate of ξR, reverting to the Susceptible state, potentially re-entering the cycle of infection.

Individualized Transmissibility Model

We hypothesize that transmissibility can vary among individuals. As outlined in Chapter Two, the number of grooming interactions an individual engages in (grooming indegree) may confer a protective effect, as evidenced by the estimated beta coefficient of -0.12 in the logistic regression model for TB detection (detail in Chapter Two). This coefficient signifies a negative association between grooming indegree and the log-odds of TB detection. I utilize this grooming coefficient of -0.12 along with the individual grooming indegree to determine the log-odds, which are later used to calculate the transmissibility factor τ as depicted in the formula below. In the Individualized Transmissibility Model, each monkey possesses an individualized adjusted transmissibility factor τ (τ*) based on their grooming behavior.

$$\log(\text{odds}) = \left(\frac{\tau}{1-\tau}\right) - (\text{groom coefficient x individual's groom indegree})$$

$$\tau^* = \frac{exp(log(odds))}{1+exp(log(odds))}$$

Individualized Latency Model

We hypothesize that the duration an individual remains in the Exposed state (latent period) could be influenced by certain individual factors. One such factor investigated is the grooming indegree of each individual (as shown in Chapter Two). The estimated beta coefficient from the logistic regression model of -0.12, represents the association between grooming

indegree and the log-odds of transitioning from the Exposed to Infectious state. I utilize this grooming coefficient of -0.12 along with the individual grooming indegree to determine the log-odds, which are later used to calculate the individualized σ (σ^*) as depicted in the formula below. Each latent period is calculated as $1/\sigma^*$.

$$\log(\text{odds}) = \left(\frac{\sigma}{1-\sigma}\right) - (\text{groom coefficient x individual's groom indegree})$$

$$\sigma^* = \frac{exp(log(odds))}{1+exp(log(odds))}$$

In the baseline model, each monkey possesses the same baseline transmissibility rate (τ). Their potential for contracting TB is influenced by neighboring monkeys that are infected (α). Conversely, in the Individualized Transmissibility Model, the transmissibility rate for each monkey is individually adjusted based on their grooming behavior. Thus, the infection potential is determined by this adjusted transmissibility rate, τ^*, and the number of infected neighbors, given by the formula $1 - (1 - \tau^*)^{\alpha}$. Both the baseline model and the Individualized Transmissibility Model transition from the Exposed state to the Infectious state at the baseline rate, σ.

Building on this, the Individualized Latency Model assigns all monkeys the same baseline transmissibility rate. Hence, their variation in likelihood of contracting TB primarily depends on proximity to infected neighbors. However, this model uniquely assigns each monkey an individualized latency rate, which is adjusted based on their grooming behavior. Thus, their transition from the Exposed state to the Infectious state dictates as σ^*E.

The values for these parameters, which I estimated based on previous research and optimization methods (Brent, 2013), can be found in Table 3.2. I established baseline transmissibility from insights from natural infections in long-tailed macaques (Warit et al.,

2020b). Subsequently, in my Individualized Transmissibility Model, this value was allowed to range from 0.16 to 0.87, accounting for the variability associated with grooming indegree values.

Baseline of latency period was set at seven months (Walsh et al., 1996). To incorporate the diverse buffering effects, my Individualized Latency Model introduced variations by accommodating latency periods spanning from 38 days to 3.7 years. The estimated infection period was set at one month, a parameter derived from observations in experimental laboratory monkeys whose chest X-rays became clear even after they initially showed signs of infiltrate (Capuano et al., 2003b). In determining the duration of immunity, I drew upon data from a virtual population study (Joslyn et al., 2022), which closely aligned with findings in long-tailed macaques (Cadena et al., 2018). By employing these individualized approaches, I can personalize the simulation to examine how grooming behavior influences the likelihood of infection or disease progression for each individual separately.

Table 3.2 represents parameter estimates for each model.

Parameters	**Baseline Transmission Model**	**Individualized Transmissibility Model**	**Individualized Latency Model**
Transmissibility (τ)	0.36	0.16 – 0.87	0.36
Latent period ($1/\sigma$)	7 months	7 months	38 days – 3.9 years
Infectious period ($1/\gamma$)	1 month	1 month	1 month
Immunity period ($1/\xi$)	16 weeks	16 weeks	16 weeks

Simulation procedure and chance of infection analysis

In my exploration of TB infection dynamics across various models, I delved into the calculation of reinfection occurrences for each individual. To ensure accuracy, I extended the simulation duration by conducting 1,500 time steps and excluded the initial 500, which can be

considered as the simulation burn-in or warm-up phase. This approach allowed me to focus on the period when the disease dynamics had stabilized, providing a more reliable basis for my analysis (Huynh et al., 2015).

To examine the impact of social buffering through grooming on the likelihood of contracting TB, I analyzed the relationship between chance of infection and grooming indegree for each mode. This analysis involved computing the chance of infection, which reflects the frequency of reinfections within the population over a specified time period (1000t). I conducted 100 simulation iterations, each tracking disease dynamics up from t =501 to t = 1500. In each iteration, I selected a random individual to initiate infection. After completing all simulations, I aggregated these instances from all iterations to calculate the mean value, resulting in the chance of infection. This average value serves as an indicator of infection potential within my models and provides insights into the relationship between an individual's centrality, represented by grooming indegree, and the probability of infection. Following this, I employed Generalized Linear Models (GLM) to examine the role of grooming indegree in predicting the chance of infection for each model.

Results

In order to explore the connection between groom indegree and the probability of infection, I employed three distinct models: the Baseline Transmission Model, the Individualized Transmissibility Model, and the Individualized Latency Model. Figure 3.2 visually represents the changes in the number of individuals in each state from t501 to t1500 across 100 simulations. Additionally, it features scatter plots that depict the relationship between groom indegree and the chance of infection.

The Baseline Transmission Model yielded an average infection rate of 7.9% ± 2.8%. The GLM analysis demonstrated a positive relationship between groom indegree and the chance of infection ($\beta = 0.05$, p-value <0.001). This result suggests that individuals with higher groom indegree exhibit an elevated susceptibility to infection.

Similarly, in the Individualized Transmissibility Model, the average infection number is 7.8 ± 2.8%, indicating a strong relationship ($\beta = 0.04$, p-value <0.001) between groom indegree and the chance of infection. This reinforces the observation that the chance of infection is higher in individuals with higher groom indegree.

In the Individualized Latency Model, the average infection number is 9.01 ± 3.1%. Contrary to the previous models, the GLM analysis in this case revealed a significant inverse relationship ($\beta = -0.19$, p-value <0.001) between groom indegree and the chance of infection, suggesting that individuals with higher groom indegree have a lower likelihood of infection in this context.

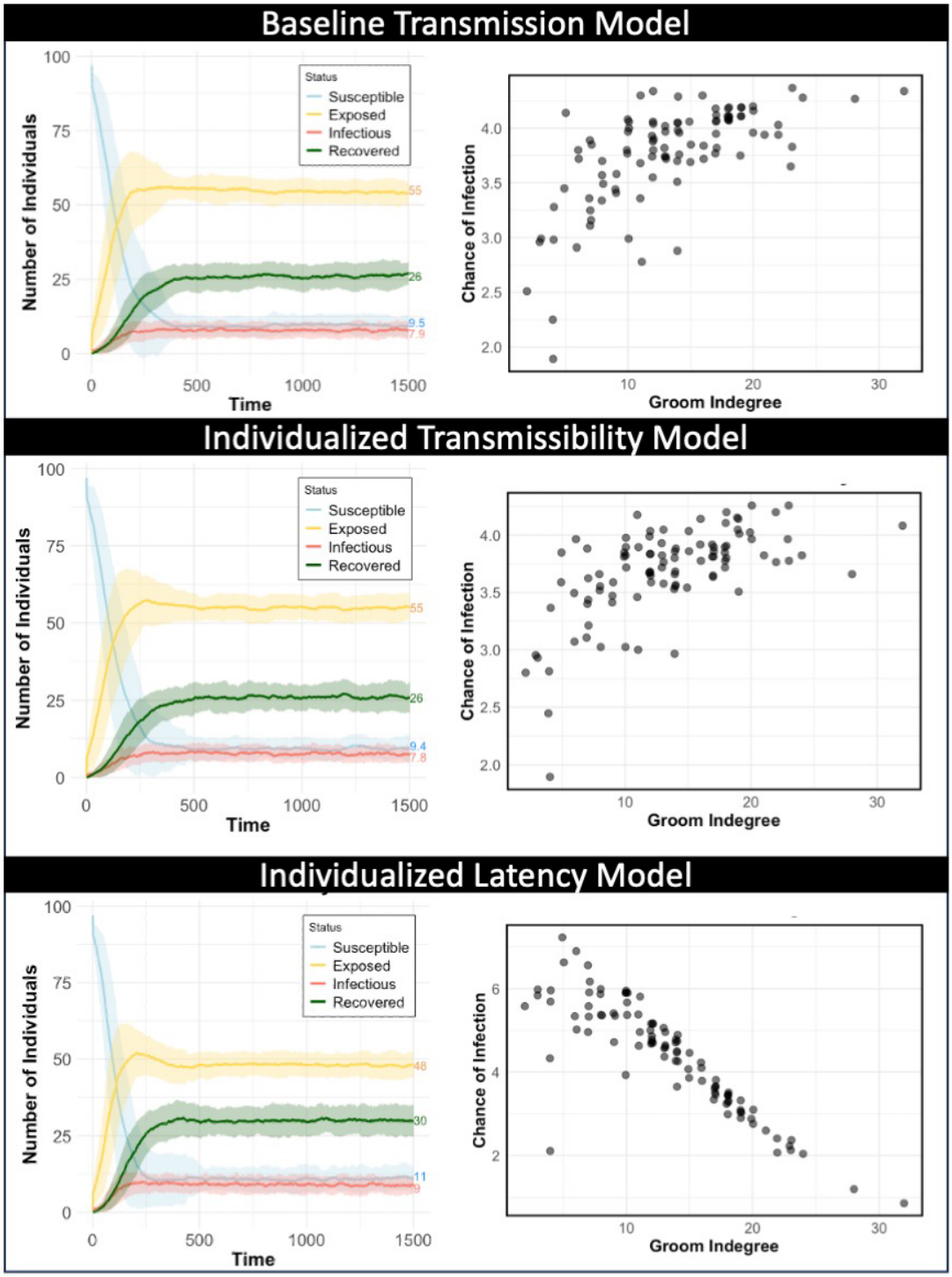

Figure 3.2 Left: The changes in the number of individuals in each state across 100 simulations. The numbers displayed on the rightmost represent the average number in each state from t501 to t1500. Right: The scatter plots of the relationship between groom indegree and the chance of infection

Discussion

In the realm of wildlife disease transmission, our understanding has traditionally relied either on laboratory-focused studies for TB diagnostics (Capuano et al., 2003b; Lin & Flynn, 2012; Warit et al., 2020b) or hypothetical epidemiological models (Erinle-Ibrahim et al., 2021; Mettle et al., 2020a; Ozcaglar et al., 2012). However, there is a notable gap in research that effectively bridges the divide between studying actual infection status and examining how diseases propagate through wildlife social networks. In this study, I address this critical gap by developing and applying epidemiological models to observe the dynamics of TB infection in a group of free-ranging long-tailed macaques. By integrating theoretical modeling with real-world network data, I aim to provide valuable insights into the spread of infectious diseases in wildlife populations, offering a holistic perspective on disease transmission dynamics.

Building upon the classic SIR model, which assumes an equal probability of state change for all individuals within a population, my study acknowledges that animals, particularly a primate that lives in complex social groups, engage in non-random and heterogeneous interactions driven by their interconnectedness within their networks (Bansal et al., 2007b). In this context, I have developed an SEIRS model on an empirical network to investigate the dynamics of TB infection in long-tailed macaques. This model considers the latent period during which individuals are exposed to the pathogen but are not yet active (Mettle et al., 2020b), as well as reinfection, where immunity after recovery is temporary, and recovered individuals can lose immunity and return to a susceptible state (Erinle-Ibrahim et al., 2021). Moreover, I have incorporated individualized transmissibility and latency periods, considering the social buffering effect stemming from grooming interactions. These extended models provide a more precise

representation of how disease spreads through social networks by considering that individuals may have different risks and disease progression profiles.

In my first model, the Baseline Transmission Model, I incorporate all baseline parameters (detailed in Table 3.2). Individual variations in infection potential primarily arise from direct contact with infected individuals within the proximity network. Building upon this foundation, my second model, the Individualized Transmissibility Model, considers not only proximity to infected neighbors but also individualized transmissivity driven by the buffering effect of grooming interactions. Lastly, the third model, the Individualized Latency Model, retains baseline transmissibility while allowing for adjustments to the latency period. This adjustment represents the variation in the duration an individual remains in the exposed state before transitioning to the infectious phase. These models collectively provide a comprehensive framework for examining the intricacies of disease transmission within social networks and offer valuable insights into the spread of diseases in wildlife populations.

The average infection prevalence obtained from all three models (Baseline Transmission Model: 7.9 ± 2.8%, Individualized Transmissibility Model: 7.8 ± 2.8%, Individualized Latency Model: 9.1 ± 3.1%) consistently mirrors the real-world data, which indicates an approximate prevalence of 11% within this population and a prevalence rate of 9% in other populations of common long-tailed macaques (calculated from Meesawat, 2023b, in populations where at least one individual tested positive). Because the Baseline Transmission Model is constructed based on the concept of contact transmission, the likelihood of infection is higher among monkeys that engage in more frequent grooming interactions. These findings, however, do not align with the data presented in Chapter Two, which demonstrates that within this population, monkeys receiving less grooming tend to have a higher likelihood of infection.

We have considered two potential mechanisms to explain why infected individuals are often located in the periphery of the social network. First, I propose the concept of a social buffering effect, where monkeys with strong social bonds may be protected when exposed to pathogen and are less likely to transition from a susceptible state to an exposed state (Individualized Transmissibility Model). Second, I suggest that social buffering could also prolong latency period, protecting individuals from transitioning from an exposed state to an infectious state (Individualized Latency Model).

Interestingly, the results from the Individualized Transmissibility Model indicated that even when I accounted for social buffering from a susceptible state to an exposed state, it still revealed a high likelihood of infection among monkeys that engage in frequent grooming interactions. In other words, varying transmissibility values did not correspond to the chances of infection. In contrast, the results from the Individualized Latency Model reveal a contrary trend, with a markedly reduced probability of infection observed in monkeys with greater grooming interactions. This observation is consistent with the findings of this population from Chapter Two, that monkeys who have fewer grooming partners are more likely to be infected. This suggests a critical role for social buffering, particularly during the latency period, and lends substantial support to the Individualized Latency Model.

The observed behavior in the Individualized Transmissibility Model, where infected individuals appear to be more social despite the incorporation of a buffering effect on transmissibility, can be better understood by considering the complex relationship between transmissibility (τ) and the overall infection potential (β). According to the formula $\beta = 1 - (1 - \tau)^{\alpha}$, the impact of transmissibility (τ), is contingent on the value of the number of surrounded infected individuals in the network (α) (Bjørnstad, 2018). Figure 3.3 illustrates the relationship

between the overall infection potential (β) and transmissibility (τ) at different numbers of infected neighbors (α). Changes in transmissibility's effect on the overall infection potential can be influenced by the number of infected neighbors, suggesting that the variation in transmissibility within the network might have a limited role in shaping disease transmission dynamics, with the number of infected neighbors potentially playing a more prominent role in disease progression. Considering that over half of the population experiences latency (as shown in Figure 3.2), it becomes evident that variations in transmissibility alone may not be the primary determinant of disease dynamics. Even when I adjusted disease transmissibility based on social buffering, the model still suggested that individuals with more connections were more likely to become infected, which contradicts the real-world observations in this population.

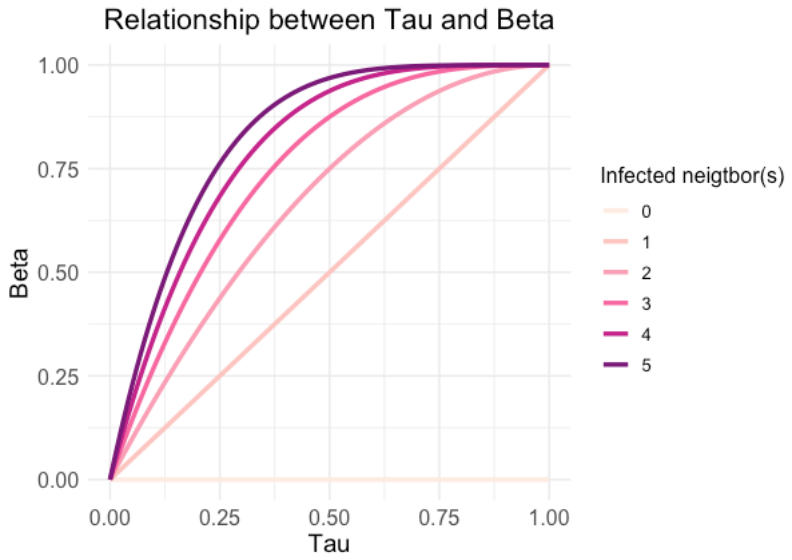

Figure 3.3 illustrates a relationship between the transmissibility (τ) and the overall infection potential (β). In the absence of infected neighbors (α), β remains at zero, regardless of the value of τ. However, when α assumes a larger value, even subtle changes in τ can exert a substantial impact on β.

In diseases with substantial latent periods like TB, we should shift our attention towards understanding the transition from exposed to infectious states. My observation supports that the

transition from latency to active TB emerged as a key mechanism explaining why infected (active stage) individuals are found in the periphery of the social network. Macaques with strong social bonds could be more likely to delay progression from latent to active TB, aligning with the nature of latent TB, which can endure for months to decades in humans (C. M. Stein et al., 2019) and up to 20 months in experimental long-tailed macaques (Warit et al., 2020b).

This finding has important implications for disease management strategies. Traditionally, it was believed that individuals occupying central positions within a social network were more likely to be responsible for disease transmission. As a result, management plans often involved removing such individuals to mitigate disease spread (MacIntosh et al., 2012). However, removing individuals from central positions within these tightly-knit social macaque groups could lead to greater fragmentation within the social network, increased stress levels (Suomi et al., 1975), a reduction in social buffering, and potentially worsen disease spread. Therefore, instead of solely focusing on preventing transmission from susceptible to exposed individuals, we should shift our attention towards understanding the transition from exposed to infectious states, particularly in diseases with substantial latent periods like TB.

Limitations and future directions

Even though my SEIRS models have effectively modeled endemic TB that closely align with observed infection rates in natural TB prevalence, it is essential to acknowledge the presence of numerous unknown factors. This approach serves as a foundational framework that can be further refined and adapted to accommodate these uncertainties. Nevertheless, I expect that the qualitative relationships demonstrated by my models will remain robust.

To gain a deeper understanding of my models, it is crucial to input accurate values for the durations of latent and infectious periods, which can vary significantly among individuals. This

information is often challenging to obtain due to the high degree of diversity among animals. For instance, the duration of TB infection can be influenced by factors such as dosage (Scanga & Flynn, 2014). Even when exposed to the same dosage, animals can exhibit a spectrum of outcomes, ranging from rapidly progressive TB to prolonged latent TB (Capuano et al., 2003b). Through this individualized modeling approach, future research could provide a deeper understanding of the intricacies and variations among individuals.

In this study, I have emphasized the role of grooming as just one facet of the complex dynamics that mitigate infection risk (Balasubramaniam et al., 2016). By accessing additional data that identifies significant contributors to disease transmission such as immunity level, stress, and coinfection (Hayward et al., 2022; Mehra et al., 2011), I can enhance the applicability and precision of my models. This information can prove instrumental in developing strategies for disease control and determining the optimal frequency of data collection.

However, it is important to note that my models employ a static network structure, which may not fully capture changes in network positions over time. To address this limitation, future research could explore the use of dynamic networks to better represent the social interactions among individuals and their impact on disease transmission dynamics, especially for TB.

General discussion

The overarching goal of my dissertation is to gain insights into the mechanisms of TB transmission among free-ranging long-tailed macaques in human-wildlife interface areas. In Chapter One, I focus on the identification of infected animals and investigates how socioecological attributes, in conjunction with the macaques' interactions with conspecifics and humans, as well as their responses to stress and sickness, shape the patterns of TB infection within these social groups. Chapter Two employs a social network approach to pinpoint infected individuals and addresses the complex relationship between contact-transmission and social buffering, exploring the role of individual macaques' social network positions in their infection status. Lastly, in Chapter Three, I employ SEIRS modeling with adaptations to account for diverse transmissibility and latency periods, aiming to comprehend the dynamics of transmission and elucidate the persistence of TB in certain populations.

Our findings indicate that the likelihood of TB infection increases in individuals with high levels of interaction with humans and among monkeys who engage in less grooming activity. This confirmation is further supported by network analysis, which reveals that monkeys with fewer grooming interactions are more likely to have TB, highlighting the role of social buffering. The visualization from the SEIRS models revealed that more than half of the population is in the latent stage of TB infection. When accounting for the role of social buffering, I observed that transition from latency to active TB emerged as a key mechanism explaining why infected individuals are found in the periphery of the social network. Macaques with strong social bonds could be more likely to delay progression from latent to active TB.

Conclusions and implications for conservation

The conservation implications of my study are manifold and timely. In an era where human-wildlife interactions are becoming increasingly frequent due to habitat encroachment and urbanization, understanding both conspecific and heterospecific disease transmission dynamics is necessary. TB is not just a threat to human populations but also poses significant risks to wildlife, potentially leading to population declines and ecosystem imbalances. By pinpointing the behavioral and ecological factors that influence TB occurrence, targeted interventions can be developed to mitigate the spread of this disease. This not only ensures the health and longevity of primate populations but also safeguards local communities and ecosystems from the cascading effects of a disease outbreak.

Investigating diseases often necessitates repeated diagnostics. Traditional methods, which often involve capturing and handling animals, can be stressful and potentially alter the behaviors of animals (Camacho et al., 2017). This can restrict the incorporation of behavioral aspects into TB research concerning wildlife. However, the use of non-invasive sample collection for TB detection, specifically through IS*6110* nested-PCR, emerges as a promising tool (Meesawat, Aiempichitkijkarn, et al., 2023). This technique not only facilitates the study of infectious agent transmission in free-ranging populations (Wilbur et al. 2012b; Wolf et al. 2016) but also promotes conservation practices that are both ethical and sustainable.

The benefits of non-invasive methods are multifaceted. They minimize potential harm and stress to wildlife, ensuring that research methodologies align with conservation principles. Economically, these approaches are more viable and efficient, enabling expansive sample sizes and consistent data collection, which is invaluable for long-term studies. By reducing direct

interactions between humans and wildlife during research, the risk of disease cross-transmission is curtailed, prioritizing the safety of all involved.

Social network analysis offers a deeper understanding of how diseases propagate within a network. These findings contribute novelty to epidemiological studies, shedding light on both the costs and benefits of social connectedness. For instance, behaviors like grooming can act as a form of social buffering, potentially protecting individuals from disease expression. In future research, it would be valuable to compare different network structures in other primate groups to ascertain if similar patterns emerge. The insights gained through such comparative studies could naturally lead to the identification of wild primates that play pivotal roles in high rates of disease transmission, consequently influencing the occurrence of disease outbreaks related to various zoonotic pathogens.

Adding a simulation model through epidemiological SEIRS provides a unique tool to visualize the dynamics of disease transmission and inform critical decisions that would otherwise be challenging to make. For instance, it could help in determining the optimal frequency and quantity of samples required to effectively address issues related to false negatives, offering insights into sample collection strategies, testing intervals, and resource allocation (Davis et al., 2018).

In summary, my research offers a comprehensive understanding of both human-induced and ecological determinants that affect the prevalence of TB in wild primate populations within environments impacted by human activities. These insights are crucial for the conservation and management of interactions between humans and macaques, especially in the context of reducing zoonotic disease transmission in Thailand. My study exemplifies the power of interdisciplinary research in unraveling multifaceted ecological challenges. By seamlessly integrating behavioral

analysis with disease epidemiology, I have uncovered the nuanced dynamics of TB transmission among wild primates, emphasizing the need for holistic approaches in future conservation efforts.

While certain findings in this research pertain specifically to TB data in long-tailed macaques, the methodology employed here holds promise for broader applications. My primary goal is to understand the interplay between behavior and the nature of disease transmission within networks. Further research in this direction, incorporating additional data and refining models, holds the potential to offer valuable insights into disease dynamics and inform strategies for more effective disease control in both animal and human populations. This interdisciplinary approach, bridging mathematical modeling with empirical network data, can lead to a deeper understanding of infectious disease spread and ultimately contribute to better public health outcomes.

Limitations and considerations

My choice of a non-invasive test in this study is limited to detecting active TB cases while excluding latent ones. This decision is consistent with my research objective, which aims to establish a connection between natural behaviors in free-ranging populations and the potential for disease transmission between individuals. Nevertheless, there is a promising avenue for future research in exploring non-invasive methods for detecting latent TB. Such an approach would provide me with the means to thoroughly examine behavioral patterns and conduct multiple evaluations. Regular testing for infections could significantly enhance early detection, reducing the risk of false negatives and accurately identify the initial day of infection. To achieve a deeper understanding of disease dynamics within communities, conducting comparative analyses of individuals' or communities' social network positions before and after infection is

essential (Stattner & Vidot, 2011). These comparisons offer invaluable insights into the causal relationship between being in the periphery of the social network and the increased likelihood of infection.

Furthermore, it is important to acknowledge that several other factors, including stress, physiological attributes, and immunity levels, could potentially influence the likelihood of TB infection (Hayward et al., 2022). Unfortunately, practical constraints prevented me from directly measuring these factors in this study. If feasible, incorporating stress or immunity levels as proxies of social buffering in individualized SEIRS models could significantly enhance our understanding of disease dynamics.

Nevertheless, this approach serves as an initial step upon which to build. The heterogeneity of the transmission network uncovered by this work provides fundamental insights into how empirical network data underlie the transmission of pathogens and explain the relationship between individual interactions and the risk of infection (Sah et al., 2018b).

Supporting Information

Ethogram (Appendix S1), *MTBC* detection procedure (Appendix S2), and samples from *MTBC* positive individuals (Appendix S3) are available in Supplementary material.

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