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Tuberculosis patients at the human-animal interface: Potential zooanthroponotic and zoonotic transmission☆

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ABSTRACT

Background: Human-to-animal transmission of *M. tuberculosis (Mtb) is* reported in South Africa but there is a paucity of epidemiological data. The aim of this One Health manuscript is to describe zooanthroponotic exposure of domestic animals to TB patients, virtually all of whom had laboratory confirmed pulmonary *Mtb* disease.
Methods: This cross-sectional study was nested within two TB contact tracing studies and collected data from 2017 to 2019. TB index patients and their households in three provinces of South Africa were recruited. A questionnaire was administered to households, assessing type and number of animals owned, degree of exposure of animals to humans, and veterinary consultations. For this analysis, we compared descriptive variables by animal-keeping status (animal-keeping vs non-animal keeping households), calculated the chi square and respective *p*-values.
Results: We visited 1766 households with at least one confirmed case of TB, 33% (587/1766) had livestock or companion animals. Of non-animal-owning households, 2% (27/1161) cared for other community members' livestock. Few (16%, 92/587) households kept animals in their dwelling overnight, while 45% (266/587) kept animals outside the home, but within 10 m of where people slept and ate. Most (81%, 478/587) of people in animal-owning households were willing for their animal/s to have a TB skin test, but <1% (5/587) of animals had been skin-tested; 4% (24/587) of animal-owning households had a veterinary consultation in the past six months, and 5% (31/587) reported one of their animals dying from natural causes in the prior six months.
Conclusion: Our survey suggests that a high proportion of patients with TB live in settings facilitating close contact with domestic animal species with known susceptibility to *Mtb*. There is a substantial exposure of household animals to patients with TB and therefore risk of both transmission to, and spillback from animals to humans.

1. Background

Zooanthroponosis (human-to-animal disease transmission) of TB has been reported in wildlife, livestock, and companion animals [1–4], but there is a paucity of information on the topic. While there are many reports describing zoonotic TB [5], defined as *Mycobacterium bovis* (*M. bovis*) transmission from animals to humans, it is poorly studied in companion animals [5–8]. For this study, companion animals are

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defined as pets or animals that are kept for one's enjoyment and company. Human-to-human transmission of *M. tuberculosis (Mtb)* and risk factors for transmission and acquisition are better documented [6–8], but there are few descriptions of zoonanthroponotic transmission.

Mtb in animals is known to occur in countries with highest incidence of human TB in Africa and Asia [9]. South Africa is one of eight high burden countries and contributed 360,000 [6] people diagnosed with TB in 2019. Due to the high burden of human TB in South Africa, which affects rural populations living in close contact with livestock, often with limited or no access to veterinary services and associated disease control measures, we investigated human-animal contact that could result in zooanthroponotic TB transmission [1]. Probable zooanthroponotic transmission of *Mtb* has previously been reported in South Africa among predominantly captivate wildlife animals, using molecular typing techniques that indicated transmission from visitors to the zoo [1].

Dogs are susceptible to *Mtb* [10], indeed half of dogs with close contact to a smear positive human patient, tested positive on interferon gamma release assays to detect TB infection [11]. Cattle, likely acquiring *Mtb* from their human herders [4], are known to react positively to the tuberculin skin test and have historically been believed to recover quickly [9]. It is also known that *Mtb* can induce lesions in cattle, raising the risk of spillback to humans [9]. Humans in close contact with a cat infected with *M.bovis* developed active TB, interaction with the sick cat was their only risk of exposure to *M.bovis* [12]. Similar to humans, younger and immunocompromised animals are more susceptible to *Mtb* [13] which may lead to severe disease and increasing the risk of spillback to humans.

Household contact tracing of TB index cases is widely acknowledged as an essential step in the control of TB [14,15]. The One Health initiative recognises the interdependence of animal, human and environmental factors in the control of diseases such as TB [16]. The aim of this One Health manuscript is to describe the exposure and interaction of TB patients and their households to livestock and companion animals.

2. Methods

We utilised cross-sectional household survey data collected across two TB contact tracing studies conducted from 2017 to 2019 in three provinces [17]. The study sites were in Limpopo (Capricorn Health District), Free State (Mangaung Health District) and North West (Dr. Kenneth Kaunda Health District) Provinces of South Africa. All three health districts included households from urban, peri-urban, and rural areas. The populations of Capricorn, Mangaung and Dr. Kenneth Kaunda districts were 1,350,111, 787,012, and 772,320, respectively, and human population densities were 62.2/km^2, 79.6/km^2 and 52.6/km^2 respectively in 2019 [18].

A researcher-administered survey was conducted in households that had a TB index case during follow up visits that were part of two contact tracing studies. Household members were defined as all individuals who shared dwelling airspace by either having slept overnight at least once or shared at least two meals in the same household as the index case in the fourteen days prior to the index case's diagnosis of TB [17]. The survey tool was developed in collaboration between researchers working in the veterinary sciences and public health and collected the following information: animal species kept and respective animal counts, reason for keeping animals, whether the animals were in the house and distance of the pens from the household. Exposure relating to methods of garbage disposal, consumption of raw milk and milk products, consumption of contaminated meat, TB testing history for their animals, if any animals had been sick in the six months prior to the survey, and if they sought veterinary care, and whether livestock were taken to the slaughterhouse. We also obtained household census data, details of living conditions and if there were other members of the household that were diagnosed with TB.

2.1. Data analysis

We compared variables by households, with and without animals. For these, we calculated proportions and conducted chi-square test, with respective *P*-values. We calculated proportions of households that owned animals and their median counts, with interquartile ranges. We used Stata v 15 (StataCorp, College Station, Texas, USA) for analyses.

2.2. Ethics

All study participants gave informed consent after the nature and possible consequences of the study had been fully explained. The two TB contact tracing studies received ethical approval from the University of Witwatersrand Health Research Ethics committee and from the three province Research Committees.

3. Results

A total of 1766 households with at least one index case of TB were included across the two contact tracing studies. Most participating households (55.7%) were in Capricorn, followed by Mangaung (38.7%) and Matlosana (5.4%), (Table 1). Thirty three percent (587/1766) of households, consisting of 5515 household members, reported owning animals. Three percent (166/5515) of all household contacts, from 40 households, were diagnosed with TB, and of these households, 98% (39/40) had more than one member diagnosed with TB. The mean age of all the participating household contacts was 25.5 years (standard deviation range is 4.6–46.4 years).

The proportion of households with ≥5 people (including the index), was larger in the group with animals compared those reporting no animals (45% vs 37%, $p = 0.000$). However, the likelihood of households with and without animals of having an additional person with TB was similar (2.4% vs 2.0%, $p = 0.638$), (Table 1). Individuals living in

Table 1
Characteristics of households by animal ownership.

Variable ($N = 1766$)	Overall	HH without animals ($n = 1167$)	HH with animals ($n = 587$)	P-value
	no. (%)	no. (%)	no. (%)	
Site ($n = 1754$)				
Capricorn	977(55.7)	654(56.1)	323(55.0)	0.945
Mangaung	693(38.9)	450(38.6)	233(39.7)	
Matlosana	96(5.4)	63(5.4)	31(5.3)	
Garbage disposal ($n = 1753$)				
Burnt	812(46.3)	530(45.6)	282(48.0)	0.035
Dump	205(11.7)	123(10.6)	82(14.0)	
In the yard	23(1.3)	18(1.5)	5(0.85)	
Municipal waste	713(40.7)	495(42.5)	218(37.14)	
Total number of HH members				
1–2	455(25.8)	335(28.7)	120(20.4)	0.000
3–4	608(34.4)	399(34.2)	205(34.9)	
≥5	703(39.8)	433(37.1)	262(44.6)	
Mean age (SD)	25.5 (20.9)	25.2(20.6)	26.2(21.2)	0.012
Mean number of HH members (SD)	5.7(2.9)	5.7(3.0)	5.8(2.5)	0.000
Other HH members with TB n (%)				
No	1714/1766 (32.6)	1139/1167 (97.6)	575/587 (98.0)	0.638
Additional one person with TB	1/1766 (0.1)	1/1167(0.1)	0	
More than one other person with TB	39/1766 (2.2)	27/1167(2.3)	12/587(2.0)	

*SD=Standard Deviation.

households with livestock or companion animals were slightly older than those without (mean age, 26.2 vs 25.2 years). Overall, participating households disposed of their garbage by either burning it (46.3%) or using municipal waste disposal services (40.7%). A larger proportion of households with animals reported burning garbage (48% vs 45.6% $p = 0.035$), whereas more households without animals used the municipal waste disposal service (42.5% vs 37.1%, $p = 0.035$).

The most frequently reported animals owned by households with an index TB patient, were dogs (64.6%), cattle (12.8%), cats (11.9%) and goats (11.2%). The largest median animal household ownership counts were sheep and goats 7 (IQR of 4 to 14) and 7(IQR 4 to 12), respectively (Table 2), then cattle 5 (IQR of 3 to 11) (Table 2). There was only one household that kept horses and another one household that kept rabbits with counts of 6 and 4 animals, respectively (Table 2).

Most animals were kept in yards/pens around the household (Table 2); 45% (266/587) of the households that had livestock or companion animals had pens within a 10 m radius of where people slept and ate.

Thirteen percent (76/587) of households reported slaughtering their own livestock in the 6 months prior to the survey. Slaughtered animals included cattle, sheep, pigs, and goats. Only 11% (8/76) of those that slaughtered used the slaughterhouse, while 92% (70/76) of households slaughtered their animals at home. Two households slaughtered some of their animals at home and others at the slaughterhouse. Slaughtered animals were often shared with the community, sold for monetary gain and other ritual purposes.

Eighty-one percent (478/587) of animal-owning households were willing to have their animals tested for TB; but TB testing had been carried out in <1% (5/587) of households. Four percent (24/587) of animal-owning households had a veterinary consultation in the past six months, and 5% (31/587) reported one of their animals dying from natural causes in the prior six months. Few households (<1%) reported consuming an animal which had died after showing signs of sickness.

Households reporting not owning animals ($n = 1167$), were 66% of this study population. Among these, 6% (70/1167) reported regular consumption of raw milk, 2% (27/1167) reported taking care of other people's animals, 7% (81/1167) purchased meat from local butchers, and 32% (369/1167) consumed meat from home slaughtered carcasses. Less than 1% (12/1766) of households were missing data on animal ownership.

Table 2
Animal species kept by the household, median animal counts and place where the animals sleep.

Animals kept N = 587	Number of HH keeping animals n/ total HH no. (%)*	Median animal counts n (IQR)	Number of HH with animals sleeping in the house n (%)*	Number of HH with animals sleeping in the yard or pen around the HH n (%)*	No. of HH with animals sleeping in a field or pen far away from HH n (%)*
Cattle	75/587 (12.8)	5 (3–11)	4/75 (5.3)	67/75 (89)	41/75 (54.6)
Pigs	18/587 (3.1)	3 (1–7)	–	15/18 (83)	12/18 (66.7)
Sheep	19/587 (3.2)	7 (4–14)	–	16/19 (84.2)	10/19 (52.6)
Goats	66/587 (11.2)	7 (4–12)	3/66 (4.5)	58/66 (87.9)	29/66 (43.9)
Horses	1/587 (0.2)	6 (–)	–	1/1 (100)	–
Donkeys	8/587 (1.4)	4 (2.5–4.5)	–	7/8 (87.5)	5/8 (62.5)
Cats	70/587 (11.9)	1 (1–2)	27/70 (38.6)	44/70 (62.9)	8/70 (11.4)
Dogs	379/587 (64.6)	1 (1–2)	40/379 (10.6)	305/379 (80.5)	81/379 (21.4)
Rabbits	1/587 (1.0)	4 (–)	–	1/1(100)	–

*Note: Percentages may not add up to 100% as some HH kept more than one animal or place where animals were kept. †HH = household(s).

4. Discussion

A substantial proportion of households with at least one index TB case were likely to have close interaction with animals, suggesting opportunities for zooanthroponotic transmission but fewer of the non-animal keeping households still interacted with animals and were also exposed to zoonotic transmission of *Mtb* by consumption of raw milk and meat from home slaughtered carcasses. In our study contacts and transmission risks we report are relevant to zoonotic transmission while others are relevant for transmission to, and between, animals.

A South African study investigated *Mtb* among mostly captive wild animals using molecular typing techniques [1] at the National Zoological Garden of South Africa over a ten-year period. They detected *Mtb* isolates with a high genetic diversity in thirteen animals, a probable indicator of transmission from visitors to the zoo animals, considering that the staff undergo stringent measures of containment and screening of infectious diseases, including TB [1]. Moreover, in an extremely endemic area in Cape Town, 1% of stray dogs examined post-mortem were found to be infected with *Mtb* [11]. Additionally, *Mtb* infections at three unrelated cattle farms [13] were traced to workers with active TB [13]. Furthermore, in Berkshire, United Kingdom, ten cats (seven with culture confirmed results*)* infected with *M.bovis*, resulting in severe clinical signs and two humans that were in close contact with one of the sick cats developed active TB. Contact with the infected cat was their only risk of exposure to *M.bovis.* The genetic patterns of *M.bovis* isolates from the cultures of the cat and human were identical [12].

The current COVID-19 pandemic has drawn attention to the One Health initiative that emphasises the interdependence of the health of humans, animals, and their environments [5,16,19]. Therefore, to achieve the milestone of "ending TB by 2030" [20], further epidemiological, surveillance and genomic work is required, as well as screening of livestock and companion animals that are exposed to TB index cases.

In our study there were few households whose livestock had been tested for TB. Bovine TB, caused by *M. bovis* is a controlled animal disease and indistinguishable from *Mtb* infection by the TB skin test. TB skin testing is the responsibility of State Veterinary Services. With financial and human resources' constraints in South Africa, TB testing activities by Government are inadequate, animal owners should be encouraged to have their animals screened for TB. To achieve this, scaling up of testing capacity coupled with species identification of causative *Mtb* complex organisms is required. Veterinary inspections are not conducted on home slaughtered carcasses, hence the risk of animal diseases entering the human food chain is higher than in commercially slaughtered livestock. However, heat-treated milk by boiling and thorough cooking of meat products assists with TB control as heat kills the mycobacteria [21].

Household members' interaction with animals reported in our study suggests they could be exposed to bovine TB such as by consumption of *Mtb*-infected raw milk and meat products [22].

This study was limited by its design; it was cross-sectional and did not include observations of households without a patient diagnosed with active TB. We did not determine *Mtb* complex infection status of animals. Moreover, fieldworkers did not observe the daily activities of individual household members related to duration and frequency of exposure to animals that would assist in quantifying the probability of human to animal (or vice versa) transmission events. Furthermore, we did not collect information for risk of exposure to *M.bovis*, such as consumption of raw milk, for animal-owning households.

We recommend expanding descriptive surveys by determining *Mtb* infection status of livestock of households with TB index cases, thus broadening the understanding of TB transmission to animals, especially those in close contact with humans.

5. Conclusion

This is the first reported survey we are aware of that assesses the animal ownership and exposure of household contacts of a TB index patient. The COVID-19 pandemic has reiterated the necessity of the One Health approach, and our data suggests more research is required to assess the extent of transmission of TB from humans with TB to their livestock and companion animals.

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Declaration of Competing Interest

None.

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