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Dilution effect in bovine tuberculosis: risk factors for regional disease occurrence in Africa

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Changes in host diversity have been postulated to influence the risk of infectious diseases, including both dilution and amplification effects. The dilution effect refers to a negative relationship between biodiversity and disease risk, whereas the amplification effect occurs when biodiversity increases disease risk. We tested these effects with an influential disease, bovine tuberculosis (BTB), which is widespread in many countries, causing severe economic losses. Based on the BTB outbreak data in cattle from 2005 to 2010, we also tested, using generalized linear mixed models, which other factors were associated with the regional BTB presence in cattle in Africa. The interdependencies of predictors and their correlations with BTB presence were examined using path analysis. Our results suggested a dilution effect, where increased mammal species richness was associated with reduced probability of BTB presence after adjustment for cattle density. In addition, our results also suggested that areas with BTB infection in the preceding year, higher cattle density and larger percentage of area occupied by African buffalo were more likely to report BTB outbreaks. Climatic variables only indirectly influenced the risk of BTB presence through their effects on cattle density and wildlife distribution. Since most studies investigating the role of wildlife species on BTB transmission only involve single-species analysis, more efforts are needed to better understand the effect of the structure of wildlife communities on BTB dynamics.

1. Introduction

Bovine tuberculosis (BTB), which is a chronic disease caused by *Mycobacterium bovis* and mainly spreads via aerosol transmission [1], not only infects a wide range of domestic and wildlife mammals, but also humans [2]. Although control programmes have eliminated or nearly eliminated this disease from domestic animals in some developed countries, BTB is still widespread in Great Britain, Ireland, New Zealand and many developing countries, especially in Africa [3,4]. In fact, this zoonotic disease is still an important public health concern, and can cause severe economic losses due to livestock death and trade restrictions [4].

Africa has the highest species richness of mammals [5] and many of these mammal species can be infected by *M. bovis*. Previous studies have been carried out to investigate the roles that wildlife species play on the dynamics of BTB transmission [4,6]. Wildlife hosts are usually classified as either maintenance hosts (such as African buffalo, *Syncerus caffer* and greater kudu, *Tragelaphus strepsiceros*), spillover hosts or dead-end hosts [3,4]. However, studies investigating the role of wildlife species often only involved single-species analysis, and neglected the effects of multiple hosts and community structure on the transmission of BTB [4].

Host diversity has been postulated to influence the risk of infectious diseases [7,8]. The effect of biodiversity on disease dynamics has attracted much current

attention in the context of global biodiversity loss and increased emergence of infectious diseases [9–12]. In theory, changes in species richness or diversity in communities can lead to a dilution effect or amplification effect by changing the abundance of competent hosts or altering the encounter rates among competent hosts in a community [7]. The dilution effect, which suggests a negative relationship between biodiversity and disease risk, occurs when the incompetent host species are more likely to be present in high-diversity communities rather than in low-diversity communities. Species which are first lost from a community tend to be those that are less competent hosts [11], ultimately leaving a higher abundance of more competent species in low-diversity systems due to release from competition or predation, and thereby increase the risk for disease transmission. On the contrary, the amplification effect occurs when there is a positive correlation between disease risk and species diversity. Even though mounting evidence of the dilution effect has been reported in many different diseases [12], whether the dilution effect generally occurs is still highly disputed [10,13].

Since the ability to transmit *M. bovis* varies among different mammal species, we expect that differences in mammal species diversity are probably able to affect the dynamics of BTB transmission. We assume that a higher mammal species richness (MSR) may provide more transmission pathways for *M. bovis*, and thus facilitate the spread of the disease. On the other hand, higher MSR may exert a dilution effect and lower BTB disease risk by increasing the abundance of incompetent hosts, which are able to interfere with the pathways of transmission, or act as sinks for *M. bovis* and deflect BTB transmission away from the cattle. Here, we examine these two alternative hypotheses referring to the effect of MSR on BTB risk in Africa.

Besides wildlife species, many other factors have been identified to be responsible for facilitating BTB transmission [1,4]. At individual level, the prevalence of tuberculosis-like lesions has been found to increase with age in cattle and buffalo [14,15]. Different breeds of cattle also experience different risk of BTB [16]. At herd level, factors such as herd size and previous infection status have been identified to correlate with the probability of positive reaction to BTB test [17,18]. Cattle movements and purchase of cattle have also been identified to facilitate BTB transmission [19–22]. However, the influence of risk factors on the dynamics of BTB transmission at larger scales, such as regional scale, is not well understood. A regional analysis of the dynamics of disease transmission can promote the understanding of the epidemiological process underlying the infection pattern, and might lead to important suggestions for regional control [23]. Moreover, studies on the influence of risk factors tend to concentrate mainly on industrialized countries, whereas the epidemiology of BTB in the developing world, especially in Africa, remains largely unknown [4]. Therefore, the present study aims to test whether the dilution or amplification effect of MSR operates on BTB transmission and to examine the key factors associated with regional BTB presence in cattle in Africa.

2. Material and methods

(a) Data collection and pre-processing

The dataset of the BTB presence/absence in cattle in Africa from 2005 to 2010 was provided by the World Animal Health Information Database (<http://www.oie.int/wahis2/public/wahid.php/Wahidhome/Home>) from the World Organisation for Animal Health (OIE). During this period, some countries reported the presence of BTB only at country level, whereas other countries specified the presence/absence of BTB at a lower administrative level. The lowest administrative level of reporting was used as the level of analysis in this study. Only administrative areas that reported presence or absence in more than two consecutive years were used in the analyses. The compiled dataset has 1355 rows of BTB presence/absence data covering 15 countries and 304 administration areas over the years 2005–2010 (see the electronic supplementary material, table S1). Per year, 27.7 per cent ($\pm 11.40\%$ s.d.) of the administrative areas reported the presence of BTB.

MSR, which was defined as the total number of mammal species present in an administrative area, was calculated based on the geographical distribution of African mammals obtained from the African Mammal Databank (AMD), an atlas of medium to large mammals [24]. For each mammal species, the AMD includes two polygon coverage files, respectively describing the distribution of suitable habitat and the distribution of species occurrence at a 1×1 km resolution [24]. The ‘actual distribution’ for each species was calculated as the intersection of these two distribution maps [25]. Since the distribution data of small mammals are usually unreliable [26], and also small mammals are less often involved in BTB transmission in Africa, only species with an average body mass greater than or equal to 2 kg from the AMD were used in the analysis. The presence (1) or the absence (0) of each species was recorded in each administrative area using the ‘actual distribution’ calculated from the AMD. The presence–absence data were compiled to calculate the total number of species or species richness of each administrative area.

Other influencing variables were categorized into biotic and abiotic variables (table 1). For biotic variables, cattle density and previous infection status have been linked to BTB risk at herd level in previous studies [17,21]. We tested whether these effects also influenced the probability of BTB presence at regional scale. Human population density was also used as a biotic predictor variable, as human population density could be considered as an indicator of trade activity [27], which has been proved to be positively related to BTB disease risk [19,20]. Also, since maintenance hosts can maintain the pathogen in the community without any other species and are able to play important roles in disease persistence, transmission and spread [3,6], we used the percentage of the area occupied by African buffalo and greater kudu as predictor variables to test the effects of these two maintenance host species. We calculated the mean cattle density (CattleD), the mean human population density (HumanD) and the percentage of the area occupied by African buffalo (Buffalo) or greater kudu (Kudu) for each administrative area. We also collected information on the infection status in the preceding year (PreInf); if BTB presented in the preceding year, PreInf was specified as 1, otherwise it was reported as 0. Since BTB disease can be transferred to a neighbouring area from an infected area through the borders they share, we calculated, for each administrative area, the percentage of the border that was shared with neighbouring infected areas in the preceding year (BorPre).

Because *M. bovis* is associated with several wildlife species [3,6], environmental factors that can influence the distribution of wildlife populations may also play significant roles in disease transmission [27,28]. We assume that a lower mean precipitation in the driest month might be correlated with a higher probability for animals to assemble at water resources or under tree-shaded areas [29,30], which can increase BTB transmission. Since previous studies have shown that *M. bovis* can survive longer under relatively colder conditions [29], we expect that lower annual mean temperature might increase the probability of the persistence of BTB. Therefore, the mean annual temperature (TemMean), the mean precipitation in the driest month (PreDry) and the mean

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Table 1. Description and summary (mean \pm s.d.) of the predictors used in the analysis, with unit, year and their predicted effects.

description of datasets	abbreviation	predicted effect	unit	year	mean \pm s.d.
biotic variables					
previous infection status	PreInf	positive	no unit	2005–2009	
mammal species richness	MSR	negative	no unit	1999	49.70 \pm 29.23
cattle density	CattleD	positive	km ⁻²	2005	13.55 \pm 18.70
human population density	HumanD	positive	km ⁻²	2006	334.5 \pm 925.7
percentage of the border shared with previous infected areas	BorPre	positive	no unit	2006–2010	70.9 \pm 35.0
percentage of area occupied by buffalo	Buffalo	positive	no unit	1999	36.3 \pm 40.9
percentage of area occupied by kudu	Kudu	positive	no unit	1999	6.6 \pm 20.1
abiotic variables					
annual mean temperature	TemMean	negative	°C	1950–2000	23.91 \pm 4.29
mean precipitation in driest month	PreDry	negative	mm	1950–2000	6.86 \pm 8.41
mean annual aridity index	Aridity	negative	no unit	1950–2000	0.61 \pm 0.34
interaction variables					
cattle density \times mammal species richness	CattleMSR	negative	km ⁻²		
buffalo \times mammal species richness	BufMSR	negative	no unit		
kudu \times mammal species richness	KuduMSR	negative	no unit		

annual aridity index (Aridity) were also calculated for each administrative area as abiotic predictor variables.

In addition, three interaction terms—MSR associated with the three maintenance host species (cattle density, percentage of area occupied by African buffalo and greater kudu)—were taken into account to test the prediction that higher MSR might weaken the effects of the maintenance hosts due to the dilution effect. The data for all predictor variables were acquired from existing databases (see the electronic supplementary material, table S2). All data pre-processing analyses were conducted in ARCGIS v. 10.0.

(b) Statistical analysis

Generalized linear mixed models (GLMM) with binary response (logistic regression models) were used to examine the effects of predictors on the probability of BTB presence both for the whole period and for each year. Only the BTB presence/absence data from 2006 to 2010 were used as a dependent variable, because the earliest year in the dataset was 2005, which was used as previous infection status (PreInf) for 2006. Before performing the GLMMs, we log-transformed MSR, Buffalo ($\log(\text{Buffalo} + 0.5)$), Kudu ($\log(\text{Kudu} + 0.5)$) and BorPre ($\log(\text{BorPre} + 0.5)$), to obtain distribution closer to normal distribution. Using GLMMs with country and year as random factors (in analyses for each year, only country was used as random factor), univariate analyses were first performed to identify the potential risk factors. The area of the unit (Area) was retained in the model as an obligate variable to correct for the effect of area size. Variables with a p -value of less than 0.25 were identified as potential risk factors, which were used to construct multiple regression models. Before fitting the multiple regression models, we assessed the multi-collinearity by examining the variance inflation factor of the candidate variables. The results of multi-collinearity test suggested little collinearity among variables (see the electronic supplementary material, table S3). For analysis of the whole period, we constructed the final multiple model using both forward and backward selection procedures, where the likelihood ratio test was applied to test for difference in the fit of the nested models. The final model for the whole

period was then fitted to each individual year to check for consistency of the effects of the predictors. After fitting the multiple regression models, we tested the spatial autocorrelation of the residuals using Moran's I index, and found little evidence for spatial autocorrelation (see the electronic supplementary material, table S4). In GLMMs with binary response, a fully standardized regression coefficient (b_M^*) was used to compare the impacts of different variables [31].

Based on the results of the final multiple GLMM, a regression-based path analysis was conducted to examine the interdependencies of the predictors and their direct and indirect effects on BTB presence [32]. A recursive conceptual path model was constructed (figure 1). Besides the variables TemMean, PreDry and Aridity, the mean annual precipitation (PreMean) and the mean temperature in the hottest month (TemMax) were also included as climatic variables, because they could be considered as measures for the suitability for human, cattle and wildlife. To reduce the climatic variables, we first conducted a factor analysis to extract the primary components. The final parsimonious path model was constructed based on W -statistic and χ^2 tests [33]. Again, the area of the unit (Area) was always retained in the model to correct for the effect of area size. Path coefficients were also calculated using a fully standardized (logistic) regression coefficient to compare the strength of the effects on continuous and binary endogenous variables [31]. All statistical analyses were conducted in R v. 2.14.0 with appropriate packages.

3. Results

(a) Regression analysis

Based on the results of univariate analyses (see the electronic supplementary material, table S3), six out of 10 variables, namely PreInf, CattleD, BorPre, Buffalo, Kudu and PreDry, were identified as potential risk factors, which were used to construct the multiple regression models. In addition, in order to test the dilution effect of MSR, we also included three interaction terms (table 1) and MSR to construct the

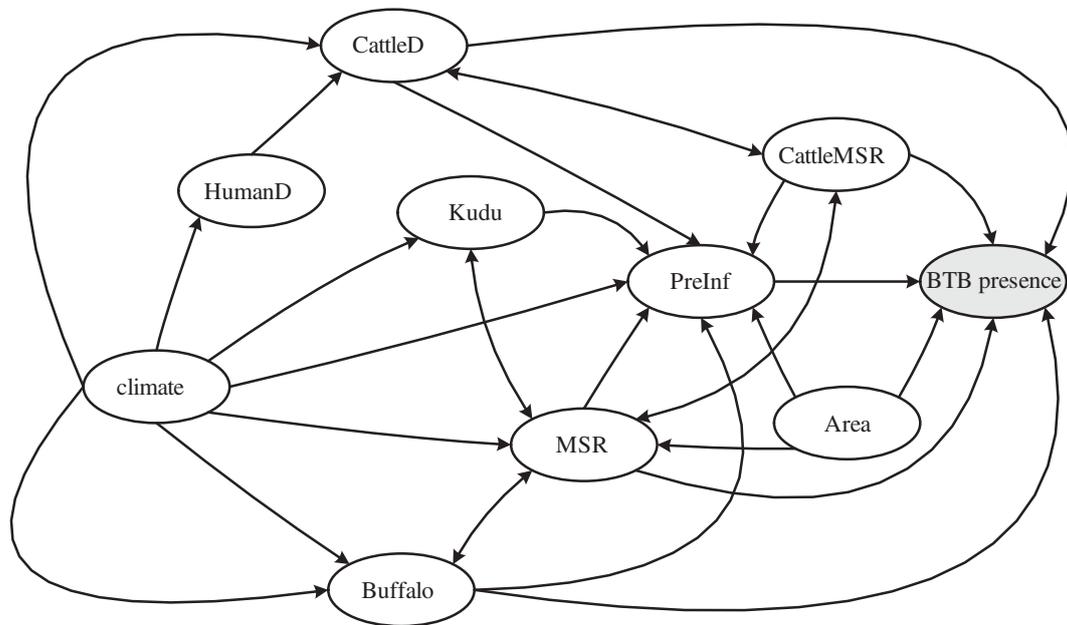


Figure 1. Conceptual path model of the potential relationships between risk factors and BTB presence.

Table 2. Multiple regression analyses of risk factors associated with the probability of BTB presence in Africa for both the whole period 2006–2010 and each year. b_M^* is the fully standardized regression coefficient.

variables ^a	predict effect	whole period						
		b_M^*	p -value	2006 b_M^*	2007 b_M^*	2008 b_M^*	2009 b_M^*	2010 b_M^*
Area	positive	0.04	0.175	−0.08	−0.05	0.26*	−0	0*
PreInf	positive	0.37	<0.001***	0.42***	0.36***	0.52***	0.37***	0.38***
CattleD	positive	0.93	<0.001***	0.31	1.99***	1.64**	1.55*	1.56*
Buffalo	positive	0.21	<0.001***	0.42***	0.15*	0.22	−0.04	0.05*
MSR	negative	−0.19	0.053	−0.26	−0.004	−0.14	0.02	0.02
CattleMSR	negative	−0.88	0.001***	−0.25	−1.97***	−1.63**	−1.62*	−1.61**

^aVariables are the area of the units (Area), previous infection status (PreInf), cattle density (CattleD), percentage of the area occupied by buffalo (Buffalo), mammal species richness (MSR) and the interaction term cattle density \times mammal species richness (CattleMSR).

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

multiple regression models. Backward and forward selection procedures generated a similar final multiple regression model. This final model (table 2) showed that the interaction of cattle density and MSR (CattleMSR) was the only interaction term that had a significant effect ($b_M^* = -0.88$; $p = 0.001$). The negative regression coefficient of CattleMSR indicated that the positive effect of cattle density was, as predicted, weaker under higher MSR than under lower MSR. The final model also identified previous infection status (PreInf), cattle density (CattleD) and the percentage of the area occupied by African buffalo (Buffalo) as significant risk factors in the prediction of regional BTB presence, all with positive regression coefficients as we predicted (table 2). Cattle density (CattleD) had the strongest effect, with a $b_M^* = 0.93$ ($p < 0.001$). In addition, our analyses also identified that country was a significant random factor ($\chi_1^2 = 70.5$, $p < 0.001$). The predictive accuracy of the final multiple model is 86.8 per cent by using a cut-off of 0.5.

The results of the regression analyses (table 2) for each year identified that previous infection status (PreInf) was a strong predictor for the probability of BTB presence for all

years. The interaction of cattle density and MSR (CattleMSR) was negatively associated with BTB presence from 2007 to 2010. The results also suggested that cattle density (CattleD) showed a significant positive correlation with the probability of BTB presence for all years except for 2006. Only in 2006, 2007 and 2010 was the percentage of area occupied by Buffalo (Buffalo) identified to be positively associated with BTB presence (table 2).

(b) Path analysis

The results of factor analysis for the climatic variables showed that the first two component axes, Factor 1 and Factor 2, respectively explained 55.6 per cent and 33.4 per cent of the variation in climatic variables. PreMean, PreMin and Aridity were heavily loaded on Factor 1, whereas TemMean and TemMax were heavily loaded on Factor 2 (see the electronic supplementary material, figure S1). A higher Factor 1 score was related to larger precipitation values, whereas a higher Factor 2 score was associated with lower temperatures.

Table 3. Summary of the effects of predictors on the risk of BTB presence in path analysis.

variables ^a	direct effect	indirect effect	total effect
Area	0	−0.04	−0.04
PreInf	0.37	0	0.37
CattleD	0.88	0.27	1.15
Buffalo	0.21	0.08	0.29
MSR	0	−0.11	−0.11
CattleMSR	−0.88	−0.24	−1.12
Kudu	0	0.09	0.09
HumanD	0	0.18	0.18
Factor 1	0	0.45	0.45
Factor 2	0	0.10	0.10

^aVariables are the area of the units (Area), previous infection status (PreInf), cattle density (CattleD), percentage of the area occupied by buffalo (Buffalo) and Kudu (Kudu), mammal species richness (MSR), the interaction term cattle density × mammal species richness (CattleMSR), human density (HumanD) and two climatic component factors (Factor 1 and Factor 2).

The path analysis confirmed the GLMM results that the interaction term CattleMSR had a negative total effect on BTB presence, while previous infection status (PreInf), cattle density (CattleD) and the percentage of area occupied by buffalo (Buffalo) had positive total effects (table 3; the final parsimonious path model is shown in the electronic supplementary material, figure S2). The human density (HumanD), percentage of area occupied by kudu (Kudu), climatic Factor 1 and climatic Factor 2 all showed positive indirect effects on BTB presence. Larger precipitation and lower temperatures were correlated with a higher risk of BTB presence through their effects on cattle density and the distribution pattern of wildlife (see the electronic supplementary material, figure S2 and table S5).

4. Discussion

Our study identified several significant risk factors that are correlated with the probability of BTB presence at regional scale in Africa. The results show that the positive effect of cattle density became weaker with increasing MSR. Administration areas with previous BTB infection, higher cattle density and larger percentage of area occupied by buffalo were more likely to report BTB outbreaks. Climatic variables only indirectly influenced BTB presence through their effects on cattle density and wildlife distribution. In addition, the results show that the variation in BTB presence was partly explained by the country, a random factor.

For density-dependent disease systems, which are usually used to describe the transmission dynamics of direct-transmitted or aerosol-borne diseases, a threshold host density or a critical community size is required for successful pathogen establishment or pathogen persistence [34]. A higher cattle density implies a higher contact rate of susceptible and infectious host individuals [35], which contributes to the persistence and spread of *M. bovis* [36]. Therefore, the probability of BTB presence is higher when cattle density increases.

A significant interaction between cattle density and MSR was shown in our study. The positive effect of cattle density

on BTB presence becomes weaker when MSR increases. Since BTB presence rather than prevalence was used as the response variable, the negative interaction between cattle density and MSR suggests that a higher cattle density is needed for the establishment and persistence of BTB when MSR is higher [34]. Therefore, this result indicates that MSR is able to dilute, rather than amplify, the impacts of cattle as maintenance host on the risk of BTB presence. This dilution effect of biodiversity on disease dynamics has attracted much attention in the context of global biodiversity loss and increased emergence of infectious diseases [8–12]. However, these studies investigating the biodiversity–disease relationships usually focus on vector-borne diseases or direct-transmitted plant diseases, while few studies were carried out on aerosol-borne or direct-transmitted animal diseases, except for hantavirus [12]. Our study detected, for the first time, the dilution effect of MSR on the risk of BTB presence, an influential aerosol-borne disease.

Two main mechanisms have been proposed for the dilution effect. One is ‘encounter reduction’, where the addition of alternative hosts may interfere with transmission pathways and reduce encounter rates between susceptible hosts and infected hosts; the other is ‘susceptible host regulation’, where interspecific competition or predation may limit the abundance of competent hosts [7]. The dilution effect we found in BTB, indicated by the negative interaction between MSR and cattle density, can be possibly explained by the ‘encounter reduction’. Previous studies suggested that transmission becomes more frequency-dependent when local transmission is integrated together across spatial scales [37]. In BTB, although many wild-life species can become infected, most of them act as spillover or dead-end hosts, and transmit the pathogen inefficiently [3,6]. The presence of these incompetent hosts might reduce the contact rates among herds by acting as barriers to herd movement, and thus increase the threshold host density and critical community size. Therefore, a higher cattle density is needed for the establishment and persistence of BTB in areas with higher MSR, which suggests an interactive effect between MSR and cattle density, as found in our study. Since we did not find a direct negative effect of MSR on BTB presence, we cannot draw a conclusion as to whether ‘susceptible host regulation’ operates in BTB in Africa. Certainly, we could not exclude the possibility that the dilution effect we detected is just caused by the correlations between MSR and some unidentified factors that we did not include in our analyses. For example, areas with higher mammal species might be nature reserves or national parks, where fences are frequently used to prevent the encounter between wildlife species and livestock. These fences can also interfere with cattle movement, and thus lead to a pseudo-dilution effect. This certainly needs further research and, ideally, experiments.

Our study also suggests that the previous infection status is a strong predictor in determining the probability of BTB presence. Being consistent with previous studies [21,38], our result indicates that BTB tends to occur repeatedly in the same area [21]. This result might be attributed to the endemicity of BTB in some areas. The difficulty in diagnosis in the early stage of the disease [29] and consistently failed control efforts [38] might also contribute to disease persistence. This result suggests that much more effort should be made to control this infectious disease in those areas that experience BTB outbreaks.

We found that the percentage of area occupied by buffalo was a predictor for BTB presence for the whole period. As a maintenance host, African buffalo plays an important role in

BTB transmission. Since African buffalo can remain infected and infectious for several years and transmit the pathogen through aerosol transmission [3], this widespread species could limit the efficiency of control measures. The movements of buffalo might also facilitate the spread of the disease, though few studies investigated this issue. Therefore, when a larger percentage of the area is covered by African buffalo, cattle will have more opportunities to come into contact with them, and thereby be more likely to experience a BTB outbreak. This result also coincides with previous studies in which the disease risk of BTB or the persistence of BTB in cattle were identified to be associated with other maintenance hosts, such as brushtail possum (*Trichosurus vulpecula*) in New Zealand [17], Eurasian badger (*Meles meles*) in UK and Ireland [18,39], and lechwe antelope (*Kobus lechwe*) in the Kafue basin of Zambia [2]. In addition, we did not find a significant direct effect of another maintenance host, the greater kudu. This might be attributed to the more limited distribution of greater kudu in Africa (13.2% of administrative areas are occupied or partly occupied by greater kudu compared with 55.3% by African buffalo).

Although other variables, such as quality of veterinary service or control measures used, could not be taken into account because of lack or incompleteness of the data, the random factor country used in the analyses is capable of controlling, to some extent, for the variation caused by these country-level variables. We admit that conclusions are usually not easy to be drawn from large-spatial-scale studies because of the complexity of the natural environment and the difficulty of controlling confounding factors [40]. The quality of the BTB presence/absence data, especially the extent, the

resolution and the accuracy, limit the precision and generality of our results. However, it is still an important step that our study was able, for the first time, to test for the importance of factors on BTB presence at regional level in Africa. Our study showed that the factors that play an important role in BTB transmission at herd level, like previous infection status and cattle density, might also be able to significantly influence BTB disease dynamics at regional level. In addition, despite the presence of many incompetent hosts in areas with higher MSR, little evidence was found that these hosts facilitate pathogen transmission and spread the disease. On the contrary, increasing MSR was correlated with lower chances of BTB presence in interaction with increasing cattle densities. Due to the limitations of our BTB dataset, this dilution effect could not be tested at lower spatial levels in our study. Further research is needed to fully reveal the effect of MSR on BTB transmission over different spatial scales. Since most studies investigating the role of wildlife species on BTB disease transmission only involve single-species analysis, it is worth increasing effort to better understand the effect of the structure of the wildlife community on the transmission of BTB [4].

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