The Hard Numbers of Tuberculosis Epidemiology in Wildlife: a Meta-Regression and Systematic Review

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Abstract

Tuberculosis (TB) is a widespread disease that crosses the human and animal health boundaries, with infection being reported in many wild species, from temperate and subtropical to arctic regions. Often, TB in wild species is closely associated with disease occurrence in livestock but the TB burden in wildlife remains poorly quantified on a global level. Through a meta-regression and systematic review, this study aimed to summarise global information on the prevalence of TB in commonly infected wildlife species and to draw a global picture of the scientific knowledge accumulated in wildlife TB. For these purposes, a literature search was conducted through the Web of Science and Google Scholar. The 223 articles retrieved, concerning a 39-year period, were submitted to bibliometric analysis and 54 publications, regarding three wildlife hosts, fulfilled the criteria for meta-regression. Using a random-effects model, the worldwide pooled TB prevalence in wild boar is higher than for any other species and estimated as 21.98%, peaking in Spain (31.68%), Italy (23.84%), and Hungary (18.12%). The pooled prevalence of TB in red deer is estimated at 13.71%, with Austria (31.58%), Portugal (27.75%), New Zealand (19.26%), and Spain (12.08%) positioning on the top, while for European badger it was computed 11.75%, peaking in the UK (16.43%) and Ireland (22.87%). Despite these hard numbers, a declining trend in wildlife TB prevalence is observed over the last decades. The overall heterogeneity calculated by multivariable regression ranged from 28.61% (wild boar) to 60.92% (red deer), indicating that other unexplored moderators could explain disease burden. The systematic review shows that the most prolific countries contributing to knowledge related with wildlife TB are settled in Europe and *Mycobacterium bovis* is the most reported pathogen (89.5%). This study provides insight into the global epidemiology of wildlife TB, ascertaining research gaps that need to be explored and informing how should surveillance be refined.

Keywords: animal tuberculosis; wildlife; bibliometric review; meta-analysis; research trends; One Health.

1 Introduction

Zoonoses are responsible for about 60% of infectious diseases emerging in humans and, in the last decades, 75% of human pathogens identified for the first time originated in animals (Jones et al., 2008). Wildlife is susceptible to the same infectious agents that affect livestock species. In several production systems across different countries, wild species share the same interface, especially in cases where livestock is managed under extensive regimes, favoring cross-transmission (Gortázar et al., 2007). The growth of the human population estimated to reach approximately 9.2 billion in 2050 (UNDP, 2008) and the expected occupation of areas for agricultural intensification, livestock production, and habitation purposes, could destroy ecological niches and habitats, disturbing the composition and structure of animal communities and food webs, thus creating opportunities for pathogen emergence and spill-over both at the intra- and interspecific levels.

Tuberculosis (TB) is a disease that interconnects the human and animal spheres, representing the One Health archetype. It is caused by a group of pathogenic mycobacteria from the *Mycobacterium tuberculosis* complex (MTC), with members associated with disease in humans (*Mycobacterium tuberculosis*, *M. africanum*, and *M. canettii*), while others are described as animal-adapted (Brites et al., 2018; Gagneux, 2018). *M. caprae* is an important pathogen that affects livestock, mostly goats, but also free-ranging wildlife (Erler et al., 2004; Reis, Albuquerque, Botelho, & Cunha, 2020; Rodriguez-Campos et al., 2011). It circulates almost exclusively in European countries, particularly in the Iberian Peninsula and Central Europe (Reis, Albuquerque, et al., 2020; Rodriguez-Campos et al., 2011). Other closely related MTC members are reported sporadically in wild species or in animals maintained in confined environments. *M. microti* is associated with infection in rodents (Kipar et al., 2014). *M. pinnipedii* with pinnipeds, such as fur seals and sea lions (Cousins et al., 2003); *M. mungi* with banded mongooses (Alexander et al., 2010); and *M. orygis* was originally isolated from African and Asian antelopes (van Ingen et al., 2012). The “chimpanzee bacillus” isolated from chimpanzee (Coscolla et al., 2013) and the “dassie bacillus” from hyrax (Mostowy, Cousins, & Behr, 2004) are

the most recently proposed members of MTC. Among the animal-adapted members, *M. bovis* is considered to have the widest host range, with cattle regarded as the main host species. However, several wildlife species in different countries and specific ecosystems are described as being able to maintain TB caused by *M. bovis* infection and to transmit the bacteria to conspecifics or other species, thus acting as reservoirs. In Europe, three species are paradigmatically affected: badger (*Meles meles*) in the United Kingdom and the Republic of Ireland; and red deer (*Cervus elaphus*) and wild boar (*Sus scrofa*) in the Iberian Peninsula (Corner, Murphy, & Gormley, 2011; Naranjo, Gortazar, Vicente, & de la Fuente, 2008; Palmer et al., 2012). The African buffalo (*Syncerus caffer*) in South Africa, brushtail possums (*Trichosurus vulpecula*) in New Zealand, Canadian bison (*Bison bison*) in Canada, and white-tailed deer (*Odocoileus virginianus*) in the USA have also been identified as TB reservoirs (Palmer, 2007, 2013). The Asian water buffalo was considered a reservoir in Australia during a limited time period (since 1970s until 1990s) (Letts, 1979). Furthermore, the possible role of other animal species as reservoirs has been the subject of research, namely elk (*Cervus elaphus nelsoni*) in USA and Canada, fallow deer (*Dama dama*) in Spain, and lechwe antelope (*Kobus leche*) in Zambia, however, their role in the epidemiology of TB is not completely understood (Fitzgerald & Kaneene, 2012; Nishi, Shury, & Elkin, 2006; Shury & Bergeson, 2011).

Altogether, *M. bovis* has been identified in ungulates, carnivores, marsupials, rodents, lagomorphs, and primates (Rodriguez-Campos, Smith, Boniotti, & Aranaz, 2014; Thoen, Lobue, & de Kantor, 2006). While several wildlife species are considered dead-end hosts, others can act as maintenance hosts for animal TB in different regions of the globe, according to the specific habitat, management conditions, host density, and genetic factors (Palmer, 2013).

Wildlife infection with *M. bovis* and transmission to livestock are pinpointed as obstacles to the success of TB eradication programs aimed to control the disease in the livestock population. Previous works reported that terminally-ill badgers and brushtail possums change their behavior to come in close contact with cattle, increasing the transmission risk by aerosol (Coleman & Cooke, 2001;

91 Corner, 2006). Furthermore, one of the main routes of transmission between brushtail possums and
92 livestock is thought to be oral rather than aerosol (Nugent, Buddle, & Knowles, 2015). Moreover, the
93 intrinsic social behavior and social organization of some wild species also contribute to intra-species
94 transmissions, such as the natural denning behavior of badgers or deer family groups composed by
95 matriarchal and several female offspring. Sharing of water holes, feeding sites, pastures, scavenging
96 of infected prey, or contamination of bites wounds are also possible routes of infection since
97 mycobacteria can be excreted in urine and feces (Corner, 2006; Corner et al., 2011; Naranjo et al.,
98 2008). Some of the infected individuals are super-shedders that excrete *M. bovis* consistently through
99 time, space, and several routes. These super-shedders give rise to higher numbers of secondary cases
100 and have been found amongst badger', wild boar', and red deer' populations (Delahay et al., 2000;
101 Santos, Almeida, Gortázar, & Correia-Neves, 2015). Numerous reports of TB in artificially managed
102 populations of red deer and wild boar in Europe or white-tailed deer in the USA have been published
103 over the years. Human interference with farming, fencing, and supplemental feeding in some
104 ecosystems, driven by economic and recreational interests, change population densities and increase
105 direct and indirect interactions, snowballing pathogen transmission (Corner, 2006; Fitzgerald &
106 Kaneene, 2012; Griffin & Mackintosh, 2000).

107 The quantification of disease burden in wildlife species susceptible to TB is crucial to design new
108 interventions and refine ongoing ones. Knowledge concerning disease prevalence in different wild
109 species, control strategies used across the world, and interactions at the wildlife-livestock interface is
110 uneven, with a persistent lack of comprehensive information regarding overall disease prevalence,
111 genotyping data, and drivers underlying TB transmission. Moreover, the distribution of TB in wildlife
112 species caused by MTC ecotypes other than *M. bovis* remains poorly known on a global level.
113 Therefore, this systematic and meta-analysis review was conducted to estimate TB prevalence in
114 wildlife, to highlight the status and geographical distribution of scientific knowledge related to TB
115 epidemiology in wildlife, and to underline the aspects that need further research. The specific aims

were to: (1) summarise global information on the prevalence of TB in commonly infected wildlife species using subgroup analyses and meta-regression; (2) clarify the spatial and temporal distribution of scientific works addressing TB in wildlife; (3) emphasize the number of works published per different wildlife host species and their geographic incidence; (4) quantify the burden exerted by different MTC members as TB agents in wildlife; (5) quantify the use of diverse diagnostic and differentiation methodologies; (6) highlight the drivers that are recognized to contribute to mycobacteria transmission in the wildlife compartment and emphasize which need further research.

2 Methods

The systematic review and meta-analysis followed the recommendations provided by the PRISMA guidelines (Supplementary Fig. 1).

2.1 Data assembly and collection

The question that guided the systematic review was “What is the current global distribution of published scientific literature concerning animal tuberculosis epidemiology in wildlife?”. The question explored in the meta-analysis was “What is the worldwide prevalence of TB in wildlife species and which are the most affected subgroups?”. To gather the peer-reviewed database, the literature search was conducted through ISI's Web of Science online interface (<http://www.isiknowledge.com>) and Google Scholar (Supplementary Fig. 1). The resulting articles were manually reviewed. Reports by national or international authorities concerning official data submitted by each country were not considered. Search results were delimited based on the following Boolean query executed within a single search. No time and geographical location restrictions were placed on these searches and only those published in English and Portuguese were retrieved. The searches were last updated on 15th April 2020.

The search strategy consisted of compiling three search strings, one for each category (tuberculosis, epidemiology, and wildlife), and combining these by the Boolean operator “AND” to obtain only the

intersection. Specifically, we used the following Boolean search statement: #1 “tuberculosis”; #2 “epidemiology”: “epidemiology” OR “transmission”; #3 “wildlife”: “Wildlife” OR “Free-range” OR “Free-ranging” OR “Feral” OR “Game” OR “Reservoir”; and the interception consisted in #1 AND #2 AND #3.

2.2 Inclusion and exclusion criteria

Results for all articles were imported into a bibliographic referencing tool and all query results were verified manually to exclude duplicate entries (Supplementary Fig. 1). The publications clearly indexed either as review, editorial, pre-prints, theses, or errata were excluded; and papers in other languages or inaccessible were also omitted (Supplementary Fig. 1).

A preliminary screening was made based on the title and abstract content of the manuscripts resulting in the elimination of the ones that did not contain information relating to TB epidemiology in wildlife. Those articles thought to have a reasonable reflection on the review questions were fully scanned and the ones not focusing on the review theme were excluded, resulting in a total of 223 articles (Supplementary Fig. 1).

2.3 Data extraction and selection criteria for the meta-analysis

After a thorough screening of the initial papers collection (223 articles), a group of 54 articles followed to meta-analysis (Supplementary Table 1). The inclusion criteria of each publication were the explicit indication of discriminated values of TB prevalence (i.e. values that were clearly discriminated by each analysed category) in each host species, obtained by any diagnostic test, and with a sample size ≥ 30 individuals. Only species containing over 10 discriminated values of TB prevalence were included for analysis. In that way, only works related with European badger, wild boar, and red deer fulfilled these criteria. Data were extracted considering author, publication year, study design (geographic location by continent and country, mammalian host), sample size, and diagnostic test used. Diagnostic tests included in the study were delayed hypersensitivity test (namely,

the tuberculin skin test), blood-based laboratory tests (namely, the interferon-gamma [IFN- γ] assay and the Enzyme-Linked Immunosorbent Assay [ELISA; includes all ELISA and ELISA-like methods independently of the used antigen]), histopathological examination (considering both macroscopic and microscopic lesions, of each examined individuals in study) and nucleic acid-based methods (that included culture since bacteriological isolation of presumptive mycobacteria is followed by molecular identification). None of the articles included in the study reported other serological assays.

The discriminated animal TB prevalence values considered were grouped as following: 1) total host population values obtained by different diagnostic tests; or 2) anatomic location of lesions per infected tract (respiratory tract, digestive tract, or generalized infection [lesions present in at least two different tracts]) (Supplementary Table 2).

To examine any effect exerted by geographic location, the study areas of all articles were grouped per continent and country and potential sources of variation were investigated using subgroup analyses; to evaluate the effect of time, three time periods were considered: 1991-2000, 2001-2010, and 2011-2020 (Supplementary Table 2).

2.4 Statistical analyses for meta-analysis

The “meta” and “metafor” libraries in R statistical package were used to estimate models for different hosts (Balduzzi, Rücker, & Schwarzer, 2019; Schwarzer, Antes, & Schumacher, 2007; Viechtbauer, 2010). All analyses were performed using RStudio (RStudio Team, 2015).

The mammalian hosts included in this meta-analysis were treated separately. The estimated prevalence values from each study were logit transformed and the pooled prevalence was estimated using a random-effects model (REM). Two model statistics were obtained, the Cochran’s Q statistic (Cochran, 1954) to test for heterogeneity and Higgin’s statistic ($I^2 > 50\%$ represents at least moderate heterogeneity) (Higgins, Thompson, Deeks, & Altman, 2003) to quantify the proportion of true variation due to heterogeneity across studies.

A univariable meta-regression model with random-effects was applied to select a group of moderator factors for multivariate analyses and to determine which percentage of heterogeneity is accounted for by each moderator. The accounted moderators were: geographic location by continent and country, publication period, sample size, diagnostic test, and anatomic location of lesions (excluded in the badger model due to lack of complete information). Multivariate meta-regression was performed to evaluate the percentage of heterogeneity accounted for by the full set of moderators. Analysis of data normality with the Q-Q plot was performed after meta-regression.

The potential evidence for publication bias was assessed by visual inspection of a funnel plot asymmetry and Begg's rank correlation (Begg & Mazumdar, 1994). The Egger's weighted regression methods (Egger, Davey Smith, Schneider, & Minder, 1997) were used to assess the significance level of the underlying bias (p -value < 0.05).

The moderator significance within the full model was obtained with an analysis of variance (ANOVA) and variables with p -value < 0.25 were retained for inclusion in the final model, as previously set in other similar reviews and meta-analyses (Dohoo, Martin, & Stryhn, 2009; Sibhat et al., 2017; Srinivasan et al., 2018).

2.5 Data analyses for the systematic review

All publications from the initial papers collection (223 articles) were included in the systematic review with the following variables retrieved: publication date, publication journal, journal subject category, document type, author, organization of origin, language, author's country of origin, title, abstract, keywords, Keywords Plus, and references. A bibliometric analysis focused on the included articles was performed using the *Bibliometrix* package in R software (Aria & Cuccurullo, 2017) and the bibliometric indicators were evaluated by authors, countries, sources, and thematic fields. The analyses of thematic fields were performed based on "Keywords Plus", indexing author' keywords for the article being indexed, but also indexing the terms derived from the titles of articles for those

that do not have author' keywords. Additionally, all articles were fully analyzed and information regarding the period of study, country of study, mammalian host, infectious agent, TB transmission drivers pointed out by the authors, diagnostic and differentiation (genotyping) methods, and the top five spoligotyping profiles were compiled and represented through descriptive statistics.

3 Results and Discussion

3.1 The present study outlines the results from a meta-analysis focused on three wildlife TB reservoirs, together with the extended bibliometric indicators of reported scientific research related to the epidemiology of wildlife TB. Meta-analysis

The selected works, that fulfilled the inclusion criteria, were published between 1996 and 2020 (24 years) and encompassed three host species, namely European badger (number of articles=17), wild boar ($n=33$), and red deer ($n=21$), with 13 articles containing data from both red deer and wild boar and two articles covering data for all three host species.

All models were assessed for publication bias regarding sample size, existence and quantification of true heterogeneity, and data normality after logit transformation. All models registered the existence of heterogeneity (Q value with p -value < 0.001), with the proportion of true variation due to heterogeneity across studies (I^2) being 99% (for badger), 99.4% (red deer), and 99.6% (wild boar). Thus, in all models prevalence varies widely across studies, with the variation appearing to reflect real differences rather than sampling errors.

3.1.1 European badger (*Meles meles*)

Publication bias was not found to be significant (Fig. 1A) and the data fit against a Q-Q plot (Fig. 1B) indicated a normally distribution. The overall mean prevalence reported for badgers was 11.75% (95% CI: 7.89%, 17.16%) (Fig. 2). Univariable meta-regression analysis of the four moderators considered (see methods) was performed. Very little of the variation between studies was explained

by publication period, diagnostic test or sample size (univariate heterogeneity (R^2) < 1.0%) (Supplementary Table 3). All the studies were conducted in Europe (the native range of badgers), so location by continent could not be considered, but within Europe, location by country accounted for 39% of the variation. All four moderators were also subjected to multivariable meta-regression analysis, accounting for 47.12% of the observed heterogeneity. Analysis of variance (ANOVA) test indicated that all moderators were significant, except sample size when all variables are considered (Supplementary Table 3).

The estimated stratified disease prevalence of moderators was calculated. When assessing geographic location as per country, both Spain (3.05%) and France (5.31%) showed a significantly lower animal TB prevalence than the UK (16.43%) and Ireland (22.87%). Both UK and Ireland show high TB prevalence in the European badger, together with high livestock TB prevalence, probably due to the high rate of contacts between cattle and badgers that result from the higher abundance, behavior and social structure of this wildlife species in its territory (Byrne, Sleeman, O'Keeffe, & Davenport, 2012; Judge et al., 2017). Additionally, UK (Northern Ireland) and Ireland share borders, facilitating the natural or artificial circulation of infected animals. Strikingly, badgers are widely distributed across Europe; but TB epidemiological information on this species is lacking from many countries, making it impossible to robustly assess the role of badger as a wildlife TB reservoir in Europe as a whole. Regarding sample size, studies performed with a lower number of individuals (100-250) showed higher disease prevalence than those focusing on a higher number of specimens (>250). Regarding the publication period, a temporal tendency was observed. Studies conducted between 1991 and 2000 showed higher animal TB prevalence (19.05%), followed by those performed between 2001 and 2010 (13.07%), and finally by those carried out more recently (2011-2020; 11.29%), which may be related with an improvement in the efficacy of control and eradication programs over the past few decades, particularly in the UK and Ireland, where the species remains a TB reservoir.

3.1.2 Wild boar (*Sus scrofa*)

Publication bias was not found to be significant (Fig. 3A) and data normality was verified by a good fit against a Q-Q plot (Fig. 3B). Focusing on wild boar works, the overall mean TB prevalence was estimated to be 21.98% (95% CI: 15.7%, 29.88%) (Fig. 4). A total of six moderators were used in the univariable meta-regression and publication period, diagnostic test or anatomical localization of lesions (univariate heterogeneity (R^2) < 1.0%) explain very little of the variation between studies (Supplementary Table 3). The multivariable meta-regression analysis accounted for 28.61% of overall observed heterogeneity, indicating that the moderators included in the regression model explain a third of the observed variability. Three moderators (geographical location per country and continent, and sample size) were considered significant (p -value < 0.25) by ANOVA test (Supplementary Table 3).

When focusing on geographic location, wild boar in Europe has an estimated TB prevalence of 23.35%, a higher value comparing to Asia (2.54%). Despite the limited availability of data concerning Asia ($n=2$), that only includes one country representing a very limited evaluation of the continent, the wild boar population has been increasing in abundance and distribution across continental Europe, justifying the importance of this species under the One Health perspective. Additionally, different resource allocation to study wildlife diseases between developing and developed countries can contribute to a well-known epidemiological scenario in Europe compared to other continents. In Europe, TB prevalence in wild boar varied between 31.68% in Spain and 9.49% in France, with Italy (23.84%), Hungary (18.12%), and Portugal (13.03%) also being remarkably affected. All studied European countries showed higher estimated TB prevalence values, with the South bioregion that is comprised of Portugal, Spain, and Italy, and where the estimation of wild boar density is higher (Enetwild consortium et al., 2019), also showed higher estimates of animal TB prevalence. Similar to the European badger model, larger sample sizes (>250) were associated with lower prevalence numbers, probably related to a more accurate assessment of estimated disease prevalence. A temporal trend in the decrease of TB prevalence was also registered across the considered periods (1991-2000,

51.72%; 2001-2010, 26.22%; 2011-2020, 19.50%) that may be related with an improvement in the control and eradication programs of animal TB over the past few decades, all over Europe. This decrease could also be related with the fact that latter works include study areas in the edge of high burden TB zones, therefore decreasing the global prevalence values obtained. Moreover, the higher number of works performed in the last two decades allows a better characterization of the TB epidemiological scenario in wild boar.

Regarding diagnostic tests, TB prevalence estimated by nucleic acid-based methods (26.66%) yielded higher values than ELISA (20.30%) and histopathology (18.63%). The reported differences result from different sensitivity and specificity characteristics of each test, together with different histopathological manifestations of the disease in this species, with microscopic lesions in early stages of disease possibly going unnoticed during the anatomopathological examination of the carcasses (Martín-Hernando et al., 2007). When considering the prevalence of TB lesions in the different tracts, the digestive tract (19.12%) was the most affected. Generalized lesions (two or more tracts) occurred in 10.33% of animals, while the prevalence of respiratory tract lesions was 6.25%. The ecological context and social structure of wild boar may explain why lesions in the digestive system and associated lymph nodes are more frequent, as these usually arise from oral ingestion of contaminated pasture, feed, water, or carcasses as the main route of infection. Contrarily to livestock and humans, transmission among wild boar is less frequently aerogenic, so lesions in the respiratory system and associated lymph nodes are not as common (Barasona et al., 2017; Cowie et al., 2016). The cases of generalized infection are most commonly found among wildlife than livestock due to the periodical *antemortem* testing of livestock, contrary to what happens in wildlife, in which the diagnostic rarely occurs *antemortem*.

3.1.3 Red deer (*Cervus elaphus*)

Publication bias was found for this model (Egger's test; p-value=0.001) towards high sample size studies (Fig. 5A). Data normality was verified by a good fit against a Q-Q plot (Fig. 5B). The mean

prevalence of TB in red deer was estimated at 13.71% (95% CI: 8.51%, 21.33%) (Fig. 6). Six moderators were included in the univariate meta-regression, with R^2 variation between 0% and 49.23%, being the higher values registered for sample size (49.23%) and anatomical localization of lesions publication period, geographic location by continent, and diagnostic test explaining very little of the variation between studies (univariate heterogeneity (R^2) < 1.0%) (Supplementary Table 3). Multi-regression was performed including all the cited moderators, accounting for 60.92% of heterogeneity. The ANOVA tests indicated that geographical location (per country and per continent), and sample size are significant in the presence of the remaining variables (p -value < 0.25) (Supplementary Table 3). Those moderators were found to have different effects on the prevalence of animal TB in red deer. According to the model, sample size with a number of individuals below 250 tended to have higher disease prevalence than those performed on a higher number of individuals (>250). No statistical differences were found in TB prevalence between Europe and Oceania, probably due to small input data from Australasian countries (only four New Zealand inputs; 19.26% disease prevalence). However, despite red deer being naturally present in Europe, contrary to Oceania where it was introduced in the second half of the 1980s (King, 1990; Lovari et al., 2018), more studies in countries where this species is considered introduced (invasive) should be performed to fully disclose the role of red deer as a wildlife TB reservoir (Nugent, Gortazar, & Knowles, 2015). Regarding the differences across European countries, Switzerland (0.18%), Italy (0.19%), and UK (1.02%) reported significantly lower TB prevalence, while France (6.42%) and Spain (12.08%) showed moderate prevalence, contrarily to Portugal (27.75%), and Austria (31.58%), which exhibit high TB prevalence rates in red deer. These differences could also result from the bias introduced by the relative weight of data reported from each country. The European countries with larger red deer population are the UK (number of individuals = 355,000), Spain ($n = 275,000$), Austria ($n = 150,000$), and France ($n = 100,000$) (Burbaité & Csányi, 2010). All of these are represented in our meta-analysis, however, no association between animal abundance and disease prevalence could be established. Furthermore, the stability of red deer harvest growth rate in Europe may be related with higher animal

TB prevalence, since European countries where the harvest growth rates have been more stable over time (Germany and Austria [Portugal not included in the cited study]) (Milner et al., 2006) show higher overall estimated disease prevalence values. Additionally, there is also evidence of winter feeding as a source of infection, due to higher indirect environmental infection in aggregation points (Nigsch, Glawischnig, Bagó, & Greber, 2019).

Regarding diagnostic tests, TB prevalence estimated through histopathology (17.15%) tend to report higher values than by nucleic acid-based methods (10.09%), probably due to differences in sensitivity and specificity of each test. Moreover, red deer normally develop purulent and/or open lesions which are more easily recognized as TB-compatible lesions during necropsy. This species may also be more susceptible to infection by several other infectious agents that cause granuloma-like lesions, such as *M. avium* subsp. *paratuberculosis* (Sleeman et al., 2009) that posteriorly are not confirmed by nucleic acid-based methods. Differential prevalence values are associated with distinct anatomical locations, with digestive tract lesions presenting a higher prevalence (46.37%), followed by generalized lesions (27.21%), and finally by respiratory tract lesions (13.76%). These results could be expected in wild deer since the oral ingestion of contaminated material is attributed as the main infection route (Barasona et al., 2017; Cowie et al., 2016). As previously discussed in the wild boar section, generalized infection cases are most commonly found in red deer (and other wild species) than in livestock due to rare *antemortem* testing of wildlife, which leads to advanced stages of the disease before a diagnosis is reached.

3.2 Systematic review

After the initial meta-analysis regarding the main wildlife TB reservoirs, an extended systematic review with the initial collection of articles (223 articles) was performed to further investigate the published scientific literature concerning animal TB epidemiology in wildlife.

3.2.1 Temporal and geographic trends

Two hundred and twenty-three documents from 64 different sources and 1044 authors were reviewed. These works cover 39 years (from 1981 to 2020) of publication, presenting an annual medium rise (that is the average number of articles published per year according to the drawn trendline) of six articles per year. The annual scientific production has been increasing over the years since 1993 (nine articles per year), with a marked growth since 2005, when the annual medium rise stands at 12 articles per year, reaching a peak between 2015 and 2019 (Supplementary Fig. 2A). The study period of the analyzed documents (i.e. the period of time to which each study relates to) ranged between 1920 and 2018, with a marked increase from 1985, reaching a peak between 1998 and 2012 (Supplementary Fig. 2B). Most studies reported a duration period of one to ten years (74.7%), followed by a duration period of 11 to 20 years (15.2%), while long-period studies (>20 years) were rare (10.1%), being mainly performed in Europe ($n=7$). The average number of citations per document was 26.97, the average number of documents per author was 0.21, and the average number of authors per document was 4.68.

The marked increase in the number of studies and publications from 2005 onward could be related with the growing interest of TB as a One Health paradigm disease and interconnected to its zoonotic potential (FAO, 2011; Gibbs, 2014), together with the international perception of animal TB as a multi-host disease system at the livestock and wildlife spheres. Funding opportunities related with research agendas from national, bi-lateral, or transnational programs contributed to encourage and financially support work under the animal TB, zoonoses, or One Health umbrellas. Additionally, the extensive badger culling program implemented in the United Kingdom between 1998 and 2005 (Bourne, 2007); the culling strategy of brushtail possums that started to be implemented in New Zealand in 2000 (Livingstone et al., 2015), and the series of harsh measures applied between 2005 and 2012 to white-tailed deer and cattle in Minnesota, USA, to re-establish the TB-free status (Cross, Heeren, Cornicelli, & Fulton, 2018), may have jointly contributed to triggering more reports in the following years, leading to an increase in the number of publications at the livestock-wildlife

interface. The recognition of wildlife species as potential TB reservoirs and sharing within the scientific community of results from attempted control strategies, such as vaccination trials, may also have helped the intensification of work in this field. Furthermore, the wildlife TB epidemiology research follows the general trend of scientific publication that was reported to rise 8 to 9% annually to 2010 (Bornmann & Mutz, 2015).

Regarding the geographic location of each study area, over 60% of studies were performed in Europe (number of articles=210), North America ($n=39$), Africa ($n=33$), Oceania ($n=26$), South America ($n=13$) and Asia ($n=6$). Moreover, a minority of studies reported combined work in different countries from different continents ($n=8$), or the study area was not identified ($n=4$). During the reviewed period, the publication rate in Europe was higher, with six articles per year, followed by one article per year in North America, Africa, and Oceania, and finally by South America and Asia that show null growth rates due to the small total number of articles in the 39 year study period. In this category (study area), the top five countries were the UK (number of articles=48), Spain ($n=44$), USA ($n=30$), South Africa ($n=21$), and New Zealand ($n=21$). All these countries have reported TB reservoirs in wildlife: badgers (UK), wild boar and red deer (Spain), white-tailed deer (USA), African buffalo (South Africa), and brushtail possum (New Zealand). These countries report a high burden of animal TB (European Food Safety Authority (EFSA) & European Centre for Disease Prevention Control (ECDC), 2019; Ortiz et al., 2014; Sibhat et al., 2017), except the USA that only reports TB outbreaks in Minnesota and Michigan, resulting mainly from the interaction between cattle and white-tailed deer (Cross et al., 2018; Miller & Sweeney, 2013; Schmitt, O'brien, Bruning-Fann, & Fitzgerald, 2002), as well as, New Zealand where besides the low disease burden there is highly relevant transmission between livestock and wildlife (OSPRI, 2020).

Taking into consideration the institutional affiliations of all authors, the authors from European and American institutions hold higher productivity, with the UK (number of publications=210), Spain ($n=190$), USA ($n=184$), South Africa ($n=100$), and France ($n=79$) positioning on the top five of

countries with more publications. Moreover, Spain (number of citations=1225), UK ($n=1068$), USA ($n=926$), Australia ($n=514$), and Ireland ($n=435$) were the top five most-cited countries. Despite their apparent lower productivity, the higher citation of papers from Australia and Ireland could be attributed to the international interest upon the control measures applied in those countries to opossums (Oceania) and badgers (UK and Ireland). This high rate of publications could also be related to the higher availability of resources in those countries to dedicate to the animal TB problematics compared to other countries.

Strong collaboration networks across European, American, and African countries are evidenced, with a marked number of collaborations between African emerging countries and American' and European' (Fig. 7). Alliances between the UK and USA (number of collaborations=13), UK and Spain ($n=12$), Spain and USA ($n=11$), UK and Ireland ($n=11$), and South Africa and USA ($n=10$), were the most frequent, corresponding to the origins of more published works and cited authors and countries, highlighting the importance of international collaborations to the success of scientific research outputs (Fig. 7). Interestingly, the works from three of the top five productive countries (UK, USA, and New Zealand) were mainly conducted through national collaborations (62%, 65%, and 93%, respectively), contrary to Spain, wherein scientific production resulted from both national (53%) and international (47%) collaborations, while South Africa production is mainly based upon international collaborations (57%). Almost half of the studies in South Africa (48%) resulted from international collaborations with the USA, which could justify the abundance of TB studies in this African country compared to its overall scientific productivity. On the other hand, the co-occurrence network analysis of authors illustrates an intense collaboration network at the national level within Spanish authors that represent *circa* 50% of the top ten of the most prolific authors.

Evaluating the affiliation of each author, the Michigan State University ($n=23$) in the USA, the University of Pretoria ($n=20$) in South Africa, the University Complutense of Madrid ($n=20$) in Spain, the University of Stellenbosch ($n=19$) in South Africa, the Institute for Game and Wildlife Research

(IREC) ($n=17$) in Spain, and the Animal and Plant Health Agency (APHA) ($n=16$) in the UK were the most highlighted institutions publishing in wildlife TB.

3.2.2 Publication Sources and Thematic Fields

The *Journal of Wildlife Diseases* (number of publications=21), followed by the *Journal of Clinical Microbiology* (JCM) ($n=19$), *Transboundary and Emerging Diseases* ($n=17$), *Veterinary Microbiology* ($n=16$), and, finally, *Preventive Veterinary Medicine* ($n=16$) are the top five publishing journals in the epidemiology of wildlife TB. Analyzing the temporal dynamics, a predominance of the JCM is evident until 2004, when the *Journal of Wildlife Diseases* and the *Veterinary Microbiology* emerged as the major publishers. From 2013, a marked increase of publications in *Transboundary and Emerging Diseases* was evident. This swap could be justified by the current focus of JCM on human health-related topics. However, the JCM (number of citations=1159) remains the most cited source, followed by the *Journal of Wildlife Diseases* ($n=633$), *Veterinary Microbiology* ($n=551$), and *Preventive Veterinary Medicine* ($n=492$). *PLOS ONE* ($n=317$) arises in the fifth place, so despite not being one of the top publishers, the works published by *PLOS ONE* on wildlife TB can be perceived as of high interest to this scientific field, for which the open-access format also possibly contributes to increased citation.

To study the temporal evolution of publication fields, the top five fields were scrutinized. “Veterinary Sciences” is the main publication field throughout the years, following the increase in the general publication area after 2004, with an average of seven publications per year. “Infectious Diseases” is the main emergent publication field since 2013, with an average of three publications per year. Thus, an increasing tendency of authors to publish in journals more related to infectious diseases, instead of general veterinary sciences editions, can be perceived.

The top five more *globally cited* papers retrieved (i.e., number of times a document that integrates the collection has been cited by any other article) are the articles reporting the use of spoligotyping as a

tool for *M. bovis* differentiation by Aranaz *et al.* (1996) ($n=189$), still used as a gold-standard method for MTC strains genotyping (Aranaz *et al.*, 1996); the description of *M. pinnipedii* as a new member of MTC by Cousins *et al.* (2003) ($n=170$) (Cousins *et al.*, 2003); the proposal of the IS6110-RFLP method by Van Soolingen *et al.* (1994) ($n=131$), used for many years as the gold-standard technique for MTC strains genotyping (van Soolingen, de Haas, Hermans, & van Embden, 1994); the epidemiological study of TB infection in white-tailed deer by O'Brien *et al.* (2002) ($n=129$) (O'Brien *et al.*, 2002); and the wildlife TB survey conducted in Spain focusing a high number of species by Aranaz *et al.* (2004) ($n=118$) (Aranaz *et al.*, 2004).

The top five more *locally cited* references (i.e., the number of times a document from the collection under analysis has been cited by other documents within this same collection) includes: firstly, the article reporting the use of spoligotyping as a tool for *M. bovis* differentiation by Aranaz *et al.* (1996) (number of citations=30) (Aranaz *et al.*, 1996); the article describing the wildlife TB survey conducted in Spain focusing a high number of species by Aranaz *et al.* (2004) ($n=28$) (Aranaz *et al.*, 2004); the risk-factor analysis of animal TB in wild boar, red deer, and fallow deer in Doñana Park by Gortázar *et al.* (2008) ($n=23$) (Gortázar *et al.*, 2008); the article by Martín-Hernando *et al.* (2007) describing TB lesions in wild boar ($n=22$) (Martín-Hernando *et al.*, 2007); and finally, the epidemiological study by Serraino *et al.* (1999) focusing on TB transmission between wild boar and cattle in Italy ($n=21$) (Serraino *et al.*, 1999).

This panel of papers reflects the interest of the scientific community in the epidemiology of wildlife TB, with particular awareness towards differentiation techniques of MTC members, together with the study of transmission networks within wildlife reservoir populations and between those and livestock populations.

According to the sampling strategy employed, the articles were divided into three groups: wildlife, wildlife-livestock, or wildlife-livestock-human. Half of the works were focused on the interface between wildlife and livestock (49.5%), followed by works exclusively related to wildlife (43.2%)

and, finally, highlighting the One Health perspective at the interfaces of wildlife, livestock, and humans (7.2%). In this assessment, wildlife-livestock interface studies have been increasing since 2005, coupled with the increasing number of wildlife-related studies, contributing to the global expansion of wildlife TB-related studies (Fig. 8A). A clear accumulation of three articles per year was registered in the publication rate of studies focusing on the interface between wildlife and livestock and of two articles per year in studies focusing on wildlife. The increase in the number of publications in this field could be explained by the growing interest in the transmission dynamics of TB at the wildlife-livestock intersection and on the application of distinctive control strategies in wildlife by different countries.

Wildlife-specific studies are the most reported in South America (100%), Africa (71%), and Oceania (58%), while in Asia (67%), Europe (55%), and North America (55%), wildlife is usually studied together with livestock (Fig. 8B). Cattle, the main livestock reservoir species of animal TB, is widespread across the world, with higher densities being reported in Asia (namely, in India, where animals are not slaughtered), in Northern Europe, and North America (namely, in Mexico) (Gilbert et al., 2018; Robinson et al., 2014). Thus, it comes as no surprise that, in those continents, the scientific production associates wildlife TB with the interaction with livestock. The studies focusing on the zoonotic potential of wildlife TB and their interaction with livestock occur at similar levels in Europe (6%), Oceania (5%), Africa (4%), and North America (3%) (Fig. 8B). In these continents, the addition of the One Health perspective led to the inclusion of humans into the equation (FAO, 2011; Gibbs, 2014), but at a slower increase in publications' rate.

3.2.3 Diagnostic and genotyping methodologies

The frequency of the most used diagnostic and genotyping methods within the works included in this review was analyzed. In the diagnostic group, histopathology (33.8%) together with nucleic acid-based methods (culture included, as isolated bacilli are subjected to molecular identification) (33.1%) were the most prevalent (Fig. 9A). Additionally, biochemical-based methods (13.5%), ELISA (9.0%),

tuberculin-based skin tests (7.7%), and IFN- γ assays (2.9%) were also used at a lower extent. Despite bacteriological culture and histopathology being the reference methodologies for the *in vitro* diagnosis of TB, while for the TB diagnosis *in vivo* the tuberculin-based assays are the gold-standard (OIE, 2018), the majority of methods used in wildlife surveillance for TB were performed *post mortem* due to the technical difficulties associated to sampling live animals. So, contrarily to the diagnosis of livestock TB, tuberculin-based assays and IFN- γ assays are rarely used in wildlife, being substituted by nucleic acid-based methods applied directly to tissues or applied to isolates after bacteriological isolation. The IFN- γ test is still rarely used in wildlife TB diagnosis, with publications being limited to Europe and Africa, possibly due to its high cost and complexity of completeness and interpretation (OIE, 2018) (Fig. 9A).

In the second group, spoligotyping together with MIRU-VNTR are both the gold-standard methods for genotyping MTC isolates (Haddad, Masselot, & Durand, 2004). Since the first description of spoligotyping, in 1997, and of MIRU-VNTR, in 2006, both methodologies have been progressively adopted (60.6% and 39.4%, respectively), while an increase in the tendency to combine both methods was detected across all continents (Fig. 9B). Since 2012, the implementation of whole-genome sequencing (WGS) analyses applied to the epidemiological component of wildlife TB is noticed ($n=9$), mainly in Europe ($n=3$), to differentiate at a fine-scale the MTC isolates from different host species and to try to infer epidemiological relationships.

Furthermore, network-based analyses have progressively been implemented in epidemiological research of wildlife TB ($n=41$ publications), particularly in Europe ($n=24$), denoting the augmented importance given to animal movement, animal interactions, host abundance, and disease epidemiology, in numerous TB ecological contexts and epidemiological scenarios.

3.2.4 Hosts and Infectious Agents

In an initial approach, the mammalian hosts reported as being affected by TB were classified as wildlife reservoirs (that is, hosts that are able to maintain infection and to transmit the mycobacteria to conspecifics or other species) or non-reservoirs according to the literature. The first group included historically acknowledged *M. bovis* reservoirs, namely badger (reservoir in UK and Ireland), brushtail possum (New Zealand), African buffalo (South Africa), red deer and wild boar (continental Europe), bison (Canada), and white-tailed deer (USA). Since the Asian water buffalo was considered a reservoir during a limited time period and it is not recorded in none of the articles in our collection, this species had been omitted from the list of species historically described to act as reservoirs. Banded mongoose and pinnipeds were also considered as reservoirs for *M. mungi* and *M. pinnipedii*, respectively. An uneven distribution between the two groups (reservoirs and non-reservoirs) was detected, with over half (57.7%) of articles reporting wildlife reservoir-based studies, 17.6% reporting non-reservoir-based studies, and 24.7% reporting data concerning both groups, reflecting not only the wide host range of *M. bovis* but also the increasing number of TB surveys in different wildlife species and the importance of animal community-based studies. In Europe and Asia, studies were mainly focused on species described as reservoirs (72.2% and 75.0%, respectively); while in the remaining continents the studies were more evenly distributed among the three categories. In Asia, reports jointly concerning both hosts are absent. In Africa, the majority of works are from South Africa and particularly the Kruger National Park, where species richness is high. In that area, several works focus on species other than buffalo to understand their role in the overall epidemiological scenario. Also, in North America, specifically in Canada and the USA, there are published reports focusing on species other than white-tailed deer and buffalo, in order to understand their epidemiological role. In Europe, most studies focus on species already described to act as reservoirs. This is the continent where the higher number of host species regarded as reservoirs is registered ($n=3$), specifically badgers, red deer, and wild boar. The published dataset from Oceania frequently concern non-reservoir hosts, also to understand their role in the whole epidemiological scenario; works in South America are more evenly distributed (40.0% reservoirs, 40.0% non-reservoirs, 20% both).

In a second approach, all reservoirs were analyzed individually. Badger was the reservoir most commonly studied (28.4%; with a publication rate of two articles per year), followed by wild boar (28%; two articles per year) and red deer (19.5%; one article per year). This highest level of publications allowed the estimation of animal TB prevalence in the presented meta-analysis. White-tailed deer (8.9%), buffalo (6.8%), brushtail possum (5.1%) were also the focus of a number of studies, with the disease in bison (2.7%), aquatic mammals (2.1%), and banded mongoose (1.3%) being seldomly reported. The attention on badger, wild boar, and red deer is congruent with the higher productivity of the UK and Spain, where these species are wildlife reservoirs of TB. The reduced number of studies focusing on non-*M. bovis* reservoirs, such as banded mongoose and aquatic mammals, is possibly related to the difficulty to survey these species, while it may also result from a classical view of animal TB affecting terrestrial mammals and being mainly caused by *M. bovis*, which biases study design and methodologies towards this ecotype and its prototypical hosts, as well as, due to a minor global economic impact of non-*M. bovis* strains. The analysis per continent shows that European studies concentrate on badgers (35.7%), wild boar (37.5%), and red deer (26.2%), African studies focus on buffalos (76.5%), North American center on white-tailed deer (90.9%), and Oceanian studies converge towards brushtail possums (66.7%), mirroring the ecological contexts in those regions.

In a third approach, all mammalian hosts were considered, independently of their role as reservoirs, and were thus grouped by taxonomical family: *Cervidae* was the most frequently published (24.8%), followed by *Suidae* (17.4%), *Mustelidae* (16.9%), and *Bovidae* (12.0%). Other mammals were less frequently reported: *Canidae* (4.8%), *Felidae* (4.5%), *Phalangenidae* (2.5%), and *Didelphidae* (2.5%). Other families were rarely studied, summing up 14.9% of unusual hosts. The geographical disparities of scientific outputs regarding family distribution across continents can be perceived as the result of the geographical distribution of specific hosts and the local importance attributed to these species as TB reservoirs.

The publications retrieved described infection by six MTC species or ecotypes: *M. bovis* (89.5%), *M. caprae* (7.3%), *M. pinnipedii* (1.3%), *M. tuberculosis* (1.0%), *M. mungi* (0.5%), and *M. orygis* (0.3%).

An increase in publication rate of nine articles per year, from 1981 to 2020, was registered for studies related to *M. bovis* and one article per year for *M. caprae*-related works. The increased number of publications reporting wildlife infections with *M. caprae* is probably related with the recent recognition of *M. caprae* as a separate species from *M. bovis* (Aranaz, Cousins, Mateos, & Dominguez, 2003), with the singularities of this ecotype (Reis, Albuquerque, et al., 2020) and also the opportunity explored by a group of researchers devoted to this more restrictive scientific niche, as *M. caprae* circulation is apparently limited to a small number of countries. *M. bovis* and *M. caprae* species were predominant in hosts defined as wildlife reservoirs, with *M. pinnipedii*, *M. mungi*, and *M. orygis* being reported exclusively in reservoirs (aquatic mammals, banded mongoose, and buffalo, respectively), *M. tuberculosis* being described in paradigmatic reservoirs and non-reservoirs (50.0% each), *M. caprae* being mainly narrated in reservoirs (78.6%), and *M. bovis* being also recovered from non-reservoirs (57.9%). In detail, *M. tuberculosis* was reported in buffalo (50.0%) and wild boar (50.0%), *M. caprae* was described in wild boar (60.9%), red deer (34.8%), and bison (4.3%), and *M. bovis* was found across all reservoirs, mainly wild boar (31.7%), badger (24.8%), and red deer (19.3%). Regarding host families, *M. tuberculosis* was found in *Bovidae* (25.0%), *Suidae* (25.0%), and *Elephantidae* (50.0%) families; *M. caprae* was found in *Bovidae* (50.0%), *Cervidae* (32.1%), *Canidae* (7.1%), *Bovidae* (3.6%), and *Camelidae* (7.1%); *M. bovis* was found across all reported families, mainly *Cervidae* (24.0%), *Suidae* (17.8%), and *Mustelidae* (14.3%).

M. bovis was the most reported infectious agent across all continents, varying between 80% and 100%, whereas *M. orygis* and *M. mungi* were exclusively reported in Africa and *M. caprae* in Europe. *M. pinnipedii* was reported in both South America and Oceania. *M. tuberculosis* was reported in Africa, Asia, and Europe. Asia only reported *M. tuberculosis* and *M. bovis*, North America only reported *M. bovis* and both South America and Oceania only reported *M. pinnipedii* and *M. bovis*.

In the articles using spoligotyping as a genotyping technique, the top five most prevalent profiles within each MTC ecotype were registered per article and analyzed. *M. bovis* genotype was predominantly identified as SB0121 (15.7% of articles), SB0120 (8.4%), SB0140 (7.8%), SB0130 and SB0265 (5.4% each); *M. caprae* as SB0157 (52.9%), SB0418 and SB1081 (11.8% each); *M. tuberculosis*, *M. mungi*, and *M. orygis* spoligotypes were only registered once: SIT33, SB1960, and SB0319, respectively. The extensive information regarding *M. bovis* also enabled geographic discrimination per continent. The SB0140 was the single spoligotype reported in Asia; SB0121 (24.0%), SB0130 and SB0140 (20.0% each) were mostly recorded in Africa; SB0121 (15.0%), SB0120 (9.2%), and SB0134 and SB0265 (6.7% each) were the most found in Europe, and SB0271 (25.0%) was the most reported in North America. Regarding Oceania, only four spoligotypes were registered with identical prevalence (25.0%), being SB0130, SB0140, SB1031, and SB1504. South America did not report any spoligotype. These results support the geographic stratification of molecular types across continents, possibly related to spillover from livestock to wildlife hosts.

3.2.5 Disease drivers

The transmission drivers (that is factors that could influence the rate of transmission) of wildlife TB most recurrently specified by the authors of the selected publications were investigated. Wildlife-livestock interactions (42.2%), management strategies (21.7%), and host features (19.9%) were the most cited drivers, followed by environmental characteristics (10.2%). Animal movements (3.0%), wildlife-human interactions (2.4%), and disease agent (0.6%) also came to light (Fig. 10). Management strategies include factors such as culling and vaccination; disease agent category considers the differential prevalence associated with different MTC members and the virulent profiles associated with mycobacteria genotypes; host features include sex, age, body condition, and population densities as some of the considered aspects.

In Europe and Africa, wildlife-livestock interactions (45.0% and 21.4%), management strategies (20.2% and 21.4%), and host features (20.2% and 35.7%) were the main transmission drivers of

wildlife TB. In Asia, wildlife-livestock interactions (66.7%) and wildlife-human interactions (33.3%) were the only specified drivers, while in South America, host features (100.0%) remained as the single specified driver. In North America and Oceania, both wildlife-livestock interactions (39.1% and 43.8%) and management strategies (26.1% and 31.3%) were the most discussed, with North America reporting environmental characteristics (21.7%) as a major driver in parallel with others (Fig. 10).

In agreement with these results, the implementation of control and eradication programs of animal TB in several countries are based, among other aspects, upon preventing wildlife-livestock interactions by fencing systems and utilization of selective feeders (Pereira, Reis, Ramos, & Cunha, 2020). However, other management procedures, such as culling and/or vaccination have been limited to specific countries and explored in particular situations.

3.3 Overview

Human conflicts with wildlife are expected to rise in the next decades. The growth of the human population and demand for food will increase areas for livestock production and expand agricultural practices, leading to deforestation, habitat destruction, and increased human- and livestock-wildlife interactions (Jones et al., 2013). Moreover, anthropogenic influence on animal densities and social behavior of several species is already marked in species of economic interest, with the implementation of artificial practices, such as confinement, fencing, supplemental feeding, or water. All these transformations in the spatial distribution, aggregation, and behavior of wildlife can increase the risks associated with animal infectious diseases, with implications in human, animal, and, ultimately, planetary health.

Animal TB is a problem of the entire ecosystem and could have an impact on the conservation of endangered species, wildlife-based tourism, game hunting, and the translocations of wildlife across multinational conservation areas (Michel et al., 2006). Previous works reported *M. bovis* infection in

two endangered species, Iberian lynx in Spain and Black Rhinoceros in South Africa, (Gortázar et al., 2008; Miller, Buss, van Helden, & Parsons, 2017). A complete view of epidemiological scenarios, with the identification of reservoirs and spillover hosts needs to be attained, so that more successful control strategies could be employed. Selective culling targeting badgers and white-tailed deer have been applied in the UK and USA, respectively (Vial & Donnelly, 2012), while vaccination trials in Spain, UK, or New Zealand have targeted wild boar, badger, and brushtail possum, respectively (Chambers et al., 2014; Díez-Delgado et al., 2018; Nugent et al., 2016), with differential efficacy and success rates. So extensive collaboration across veterinary, ecology, microbiology, epidemiology, and wildlife management experts is necessary to adaptively control wildlife diseases, as the results obtained in one ecosystem may not be transposed to or sustained in another scenario.

The information provided by works performed with badger, wild boar, and red deer enable a deeper analysis of the epidemiological scenario involving these three wildlife TB reservoirs, with the overall heterogeneity calculated by the multivariable regression analysis ranging from 28.61% (wild boar) to 60.92% (red deer). These results indicate that the considered moderators only explain part of the observed heterogeneity, with several other putative variables possibly contributing to explain TB prevalence in wildlife, such as management measures (e.g. culling strategies and vaccination), animal movements, interactions between wildlife-livestock, wildlife-wildlife, and wildlife-human, among others. These non-modelled variables were not represented in considerable frequency among the 54 articles surveyed to enable a rigorous meta-analysis and thus were not pondered in this study.

The differences between the overall prevalence of TB in each host species varied between 11.75% (badger) and 21.98% (wild boar). These high prevalence values in association with the known species maintenance of infection with conspecifics contribute to the classification of these host species as disease reservoirs, together with their implication in TB spreading to livestock and humans. Thus, surveillance and control actions towards badger, wild boar, and red deer should be considered in TB eradication programs where these species naturally occur to ensure animal and public health.

682 Additionally, further studies on these hosts should be performed in other countries where these
683 species are abundant, but where data remains scarce as, for example, the case of red deer in several
684 European countries.

685 Considering the different moderators included in the three models, geographical location by country
686 (3/3 models) and sample size (2/3) were the most statistically relevant predictors. The sample size
687 may be a bias factor in small sample size studies, overestimating wildlife TB prevalence, as
688 previously observed in the quantification of pooled TB prevalence in livestock (Ramos, Pereira, Reis,
689 & Cunha, 2020). The country variable proved to be an important moderator since specific wildlife
690 hosts can be perceived as TB reservoirs in some countries (badgers in the UK, red deer and wild boar
691 in the Iberian Peninsula and Central Europe), but spill-over species in others. These differences may
692 depend on the abundance and densities of those species, the composition and structure of natural
693 communities, and the management practices that together influence animal contact with other
694 potential TB reservoirs (livestock or wildlife). All these factors increase the possibility of TB
695 infection and maintenance in wildlife populations.

696 The general systematic review demonstrated that the most productive countries contributing to
697 knowledge related to wildlife TB epidemiology are located in Europe, with *M. bovis* being the most
698 reported MTC species on a worldwide scale (89.5%), mainly diagnosed by histopathology (33.8%)
699 and nucleic acid-based methods (33.1%). These results are similar to those reported recently
700 regarding livestock TB epidemiology investigation in the same time period (Reis, Ramos, Pereira, &
701 Cunha, 2020).

702 The knowledge of wildlife TB remains mainly centered in Europe, and in fact, the models that were
703 discussed concern European reservoirs. Therefore, other regions, such as Asia and South America,
704 need to extend their scope of research and reinforce their datasets, potentially benefiting from
705 international collaboration. Transmission drivers, the roles played by different hosts in multi-host
706 systems, and more experimental designs to test the effects of control measures are topics that still

need to be encouraged in order to inform strategic decisions by authorities and reformulate ineffective policy.

3.4 Limitations

As for any other systematic review, this bibliometric and meta-analysis assessment holds limitations since the platforms used to recover the academic literature implied the exclusion of all grey literature (i.e. books, reports, reviews, and theses). Also, the use of topic, in the Web of Science, and title, in Google Scholar, as sections to search publications limited the indexation of literature not including the search terms. Secondly, the language selection criteria excluded all works performed in languages other than English or Portuguese, leading to a linguistic bias, with the exclusion of valid literature produced in other languages. Thirdly, geographical bias can be found since animal TB research is focused on high-income countries where the disease is trying to be eradicated, but also in countries where animal TB shows high prevalence values, limiting the continental conclusions of this study. The number of publications or citations of an author or journal was used as an objective proxy for the scientific production and visibility of a given scientific topic and does not imply any value judgment for the quality or relevance of a particular study, author, institution, or publication. We thus underline that there are many significant and pertinent publications and authors that could not be ranked according to the established criteria. Having mentioned these limitations, we trust that our findings offer a valid representation of TB research outputs in wildlife at a global level.

4 Conclusions

This study provides an overview of epidemiological research in wildlife TB on a worldwide scale, reporting valuable information related to publication numbers, countries, sources, mammalian hosts, infectious agents, and transmission drivers, together with a meta-analysis that estimates the burden of TB in different wildlife reservoirs. Our findings also show the value of meta-analysis approaches for summarise global information on the TB prevalence across wildlife reservoirs; and the importance

of bibliometric methods to illustrate global research trends of animal tuberculosis epidemiology in wildlife.

During the four decades under study, several advances in geographic and thematic trends occurred. The general growth of this field of research is evident, mainly reflected in the increase of scientific production and international collaboration across European and North American countries. The literature is strongly based on European countries, short period studies (<10 years), with an emphasis on the badger as a TB reservoir and *M. bovis* infection. The focus on wildlife reservoirs identified in European epidemiological settings enabled the estimation of pooled prevalence in European badger (11.75%), wild boar (21.98%) and red deer (13.71%). Apart from this dominance of studies from Europe as a whole, countries in the top ten are grounded on Europe, Africa, North America, and Oceania, reflecting the strong international collaboration network among those continents and the geographic areas where wildlife TB reservoirs have been previously identified. Moreover, a progressive increase in the wildlife-livestock interface was denoted, with Africa, Europe, and North America being more aware of, or better equipped to lead with, the importance of wildlife reservoirs in animal TB epidemiology and the One Health perspective. Furthermore, histopathology and nucleic acid-based methods were the most prevalent diagnosis tools, while spoligotyping and MIRU-VNTR were the most applied genotyping approaches. An increase in both WGS and network analyses has occurred over the last few years, with an estimated increase trend for the next decade, which may justify a literature reappraisal in the coming years.

This work also highlights a tremendous gap in epidemiological research related to wildlife TB on a worldwide scale, mainly outside Europe. Therefore, the higher publication rates by specific countries with higher TB burdens, with ongoing eradication programs in cattle population and with differential strategies implemented for surveillance and control of TB in wildlife settings, limits the estimation of continental and worldwide TB prevalence values. This awareness is key to spot where future financial resources should be ascribed, with opportunities for international collaborations between

countries. While a clear increase of the scientific interest in wildlife TB and the livestock-wildlife interface is obvious, the advance in the number and completeness of publications integrating the wildlife, livestock and human components is still modest, revealing that probably the zoonotic potential and ecological impact exerted by this disease on wildlife species are still undervalued.

In parallel, our meta-analysis exposed that several moderators related to management, animal movements, wildlife-livestock interactions, and wildlife-human interactions, need to be consistently approached in future studies to highlight the factors that impact TB in wildlife. This perception demands financial and human resources allocation to enable the holistic integration of all dimensions concerning TB epidemiology in reservoirs. Therefore, this study also provides a useful reference for academics, veterinarians, funders, and policy decision-makers to guide future work and action.

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6 Conflict of interest statement

The authors declare that they have no conflict of interests.

7 Author Contributions

MVC conceived the study. ACR, BR, and ACP analysed the data under the regular supervision of MVC and wrote the first draft of the manuscript. MVC critically revised and readdressed all drafts. All authors gave intellectual input to the conceptualization and maturation of the final manuscript.

8 Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

9 References

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1064 **Figure 1** – Animal tuberculosis prevalence in badger: parameters of asymmetry and normality. A-
 1065 Funnel plot of logit transformed prevalence and standard error; B - Q-Q norm plot for normality
 1066 assessment.

Figure 2 - Forest plot visualization of animal tuberculosis prevalence in badger. “Total” refers to the sample size in each publication; “Events” refers to the number of TB positive animals; “Prevalence” refers to TB prevalence in each publication.

1071

1072 **Figure 3** – Animal tuberculosis prevalence in wild boar: parameters of asymmetry and normality. A-

1073 Funnel plot of logit transformed prevalence and standard error; B - Q-Q norm plot for normality

1074 assessment.

Figure 4 - Forest plot visualization of animal tuberculosis prevalence in wild boar. “Total” refers to the sample size in each publication; “Events” refers to the number of TB positive animals; “Prevalence” refers to TB prevalence in each publication.

1079

1080 **Figure 5** – Animal tuberculosis prevalence in red deer: parameters of asymmetry and normality. A-
 1081 Funnel plot of logit transformed prevalence and standard error; B - Q-Q norm plot for normality
 1082 assessment.

Figure 6 - Forest plot visualization of animal tuberculosis prevalence in red deer. “Total” refers to the sample size in each publication; “Events” refers to the number of TB positive animals; “Prevalence” refers to TB prevalence in each publication.

Figure 7 – Worldwide Collaborations. Scientific production plotted in the spectral color scale. Hot colors represent a higher number of publications. The higher number of collaborative studies are represented by darker lines.

Figure 8 – Interface analyses. [A] Number of publications according to interface type over time; [B] Percentage of publications according to interface type per continent. Dashed lines represent quartiles.

Figure 9 – Trends in methodologies per continent. [A] Diagnostic techniques; [B] Differentiation/genotyping techniques. Dashed lines represent quartiles.

Figure 10 – Drivers of tuberculosis in wildlife per continent. Dashed lines represent quartiles.

1100 **Supplementary Files**

1101 **Supplementary Table 1** – List of selected articles for meta-analysis.

REF	PY	TI	Meta-analysis
(Acevedo-Whitehouse, 2005)	2005	Genetic resistance to bovine tuberculosis in the Iberian wild boar	YES
(Alexander, 2018)	2018	Pathology of the Emerging Mycobacterium tuberculosis Complex Pathogen, Mycobacterium mungi, in the Banded Mongoose (Mungos mungo)	
(Alexander, 2016)	2016	Emerging Tuberculosis Pathogen Hijacks Social Communication Behavior in the Group-Living Banded Mongoose (Mungos mungo)	
(Amato, 2018)	2018	Molecular epidemiology of Mycobacterium tuberculosis complex strains isolated from livestock and wild animals in Italy suggests the need for a different eradication strategy for bovine tuberculosis	YES
(Andrievskaia, 2018)	2018	Genotypes of Mycobacterium bovis strains isolated from domestic animals and wildlife in Canada in 1985-2015	
(Anusz, 2017)	2017	Ante-mortem and post-mortem tuberculosis diagnostics in three European Bison (Bison bonasus caucasicus) from the enclosure in Bukowiec in the Bieszczady National Park in Poland	
(Aranaz, 2004)	2004	Bovine tuberculosis (Mycobacterium bovis) in wildlife in Spain	YES
(Aranaz, 1996)	1996	Spacer oligonucleotide typing of Mycobacterium bovis strains from cattle and other animals: A tool for studying epidemiology of tuberculosis	
(Atwood, 2007)	2007	Coyotes as sentinels for monitoring bovine tuberculosis prevalence in white-tailed deer	
(Balseiro, 2013)	2013	Spatial relationships between Eurasian badgers (Meles meles) and cattle infected with Mycobacterium bovis in Northern Spain	
(Barasona, 2014)	2014	Spatiotemporal interactions between wild boar and cattle: implications for cross-species disease transmission	YES
(Barasona, 2014b)	2014	Unmanned Aircraft Systems for Studying Spatial Abundance of Ungulates: Relevance to Spatial Epidemiology	
(Barasona, 2017)	2017	DNA Detection Reveals Mycobacterium tuberculosis Complex Shedding Routes in Its Wildlife Reservoir the Eurasian Wild Boar	YES

(Barrios-Garcia, 2012)	2012	Identification of Mycobacterium tuberculosis Complex by Histopathology and PCR in White-Tailed Deer (<i>Odocoileus virginianus</i>) in Tamaulipas, Mexico	
(Barron, 2018)	2018	A study of tuberculosis in road traffic-killed badgers on the edge of the British bovine TB epidemic area	YES
(Barron, 2013)	2013	Importance and mitigation of the risk of spillback transmission of Mycobacterium bovis infection for eradication of bovine tuberculosis from wildlife in New Zealand	
(Benton, 2016)	2016	Blood thicker than water: kinship, disease prevalence and group size drive divergent patterns of infection risk in a social mammal	YES
(Berentsen, 2011)	2011	Active use of coyotes (<i>Canis latrans</i>) to detect Bovine Tuberculosis in northeastern Michigan, USA	
(Bernitz, 2018)	2018	Detection of Mycobacterium bovis infection in African buffaloes (<i>Syncerus caffer</i>) using QuantiFERON (R)-TB Gold (QFT) tubes and the Qiagen cattletype (R) IFN-gamma ELISA	
(Biek, 2012)	2012	Whole Genome Sequencing Reveals Local Transmission Patterns of Mycobacterium bovis in Sympatric Cattle and Badger Populations	
(Blanchong, 2007)	2007	TB-infected deer are more closely related than non-infected deer	
(Boadella, 2011)	2011	Spatio-Temporal Trends of Iberian Wild Boar Contact with Mycobacterium tuberculosis Complex Detected by ELISA	YES
(Boadella, 2012)	2012	Effects of culling Eurasian wild boar on the prevalence of Mycobacterium bovis and Aujeszky's disease virus	YES
(Boardman, 2014)	2014	MYCOBACTERIUM PINNIPEDII TUBERCULOSIS IN A FREE-RANGING AUSTRALIAN FUR SEAL (<i>ARCTOCEPHALUS PUSILLUS DORIFERUS</i>) IN SOUTH AUSTRALIA	
(Bruning-Fann, 2001)	2001	Bovine tuberculosis in free-ranging carnivores from Michigan	
(Bruning-Fann, 1998)	1998	Mycobacterium bovis in coyotes from Michigan	
(Bruns, 2017)	2017	DIAGNOSIS AND IMPLICATIONS OF MYCOBACTERIUM BOVIS INFECTION IN BANDED MONGOOSES (<i>MUNGOS MUNGO</i>) IN THE KRUGER NATIONAL PARK, SOUTH AFRICA	
(Buzdugan, 2017)	2017	Quantitative interferon-gamma responses predict future disease progression in badgers naturally infected with Mycobacterium bovis	YES
(Caley, 2005)	2005	Assessing the host disease status of wildlife and the implications for disease control: Mycobacterium bovis infection in feral ferrets	
(Cano-Terriza, 2018)	2018	Management of hunting waste as control measure for tuberculosis in wild ungulates in south-central Spain	YES

(Chambers, 2010)	2010	Evaluation of a Rapid Serological Test for the Determination of Mycobacterium bovis Infection in Badgers (Meles meles) Found Dead	YES
(Cisneros, 2012)	2012	Surveillance for Mycobacterium bovis transmission from domestic cattle to wild ruminants in a Mexican wildlife-livestock interface area	
(Cleaveland, 2005)	2005	Tuberculosis in Tanzanian wildlife	
(Clifford, 2013)	2013	Tuberculosis infection in wildlife from the Ruaha ecosystem Tanzania: implications for wildlife, domestic animals, and human health	
(Corner, 2012)	2012	The distribution of Mycobacterium bovis infection in naturally infected badgers	YES
(Cosgrove, 2012)	2012	Live-trapping and bovine tuberculosis testing of free-ranging white-tailed deer for targeted removal	
(Crispell, 2019)	2019	Combining genomics and epidemiology to analyse bi-directional transmission of Mycobacterium bovis in a multi-host system	
(Crispell, 2017)	2017	Using whole genome sequencing to investigate transmission in a multi-host system: bovine tuberculosis in New Zealand	
(Csivincsik, 2016)	2016	Surveillance of Mycobacterium caprae infection in a wild boar (Sus scrofa) population in south-western Hungary	YES
(Cunha, 2017)	2017	Exposure of Threatened Accipitridae to Mycobacterium bovis Calls for Active Surveillance	
(Cunha, 2012)	2012	Implications and challenges of tuberculosis in wildlife ungulates in Portugal: A molecular epidemiology perspective	YES
(de Lisle, 2008)	2008	Isolation of Mycobacterium bovis and other mycobacterial species from ferrets and stoats	
(de Lisle, 2005)	2005	Surveillance of wildlife for Mycobacterium bovis infection using culture of pooled tissue samples from ferrets (Mustela furo)	
(de Mendoza, 2006)	2006	Bovine tuberculosis in wild boar (Sus scrofa), red deer (Cervus elaphus) and cattle (Bos taurus) in a Mediterranean ecosystem (1992-2004)	YES
(Delahay, 2007)	2007	Bovine tuberculosis infection in wild mammals in the South-West region of England: A survey of prevalence and a semi-quantitative assessment of the relative risks to cattle	YES
(Di Blasio, 2019)	2019	Animal tuberculosis in a free-ranging fallow deer in northwest Italy: a case of "lucky strain survival" or multi-host epidemiological system complexity?	
(Dippenaar, 2017)	2017	Progenitor strain introduction of Mycobacterium bovis at the wildlife-livestock interface can lead to clonal expansion of the disease in a single ecosystem	
(Dorn-In, 2020)	2020	Shedding of Mycobacterium caprae by wild red deer (Cervus elaphus) in the Bavarian alpine regions, Germany	YES

(Drewe, 2009)	2009	Pathology of Mycobacterium bovis Infection in Wild Meerkats (Suricata suricatta)	
(Duarte, 2008)	2008	Spoligotype diversity of Mycobacterium bovis and Mycobacterium caprae animal isolates	
(Duarte, 2010)	2010	MIRU-VNTR typing adds discriminatory value to groups of Mycobacterium bovis and Mycobacterium caprae strains defined by spoligotyping	
(Espie, 2009)	2009	Pulmonary Infection due to Mycobacterium bovis in a Black Rhinoceros (Diceros bicornis minor) in South Africa	
(Fico, 2019)	2019	Systemic tuberculosis by MYCOBACTERIUM BOVIS in a free-ranging MARSICAN brown bear (URSUS ARCTOS MARSICANUS): a Case report	
(Fink, 2015)	2015	Red Deer as Maintenance Host for Bovine Tuberculosis, Alpine Region	YES
(Garcia-Jimenez, 2013)	2013	Comparative Pathology of the Natural infections by Mycobacterium bovis and by Mycobacterium caprae in Wild Boar (Sus scrofa)	YES
(Garcia-Jimenez, 2015)	2015	Non-tuberculous Mycobacteria in Wild Boar (Sus scrofa) from Southern Spain: Epidemiological, Clinical and Diagnostic Concerns	
(Garcia-Jimenez, 2016)	2016	Spoligotype diversity and 5-year trends of bovine tuberculosis in Extremadura, southern Spain	
(Garcia-Jimenez, 2013b)	2013	Reducing Eurasian wild boar (Sus scrofa) population density as a measure for bovine tuberculosis control: Effects in wild boar and a sympatric fallow deer (Dama dama) population in Central Spain	YES
(Gey van Pittius, 2012)	2012	INFECTION OF AFRICAN BUFFALO (SYNCERUS CAFFER) BY ORYX BACILLUS, A RARE MEMBER OF THE ANTELOPE CLADE OF THE MYCOBACTERIUM TUBERCULOSIS COMPLEX	
(Glaser, 2016)	2016	Descriptive Epidemiology and Whole Genome Sequencing Analysis for an Outbreak of Bovine Tuberculosis in Beef Cattle and White-Tailed Deer in Northwestern Minnesota	
(Goosen, 2015)	2015	IP-10 Is a Sensitive Biomarker of Antigen Recognition in Whole-Blood Stimulation Assays Used for the Diagnosis of Mycobacterium bovis Infection in African Buffaloes (Syncerus caffer)	
(Gortazar, 2017)	2017	Animal tuberculosis maintenance at low abundance of suitable wildlife reservoir hosts: A case study in northern Spain	YES
(Gortazar, 2011)	2011	Fine-tuning the space, time, and host distribution of mycobacteria in wildlife	YES
(Gortazar, 2008)	2008	Bovine Tuberculosis in Donana Biosphere Reserve: The Role of Wild Ungulates as Disease Reservoirs in the Last Iberian Lynx Strongholds	YES
(Gortazar, 2005)	2005	Molecular characterization of Mycobacterium tuberculosis complex isolates from wild ungulates in south-central Spain	

(Gowtage-Sequeira, 2009)	2009	Evaluation of the CervidTB STAT-PAK for the Detection of Mycobacterium bovis Infection in Wild Deer in Great Britain	
(Hang'ombe, 2012)	2012	Mycobacterium bovis infection at the interface between domestic and wild animals in Zambia	
(Hauer, 2015)	2015	Genetic Evolution of Mycobacterium bovis Causing Tuberculosis in Livestock and Wildlife in France since 1978	
(Hermes, 2018)	2018	Bronchoalveolar lavage for diagnosis of tuberculosis infection in elephants	
(Hlokwe, 2016)	2016	WILDLIFE ON THE MOVE: A HIDDEN TUBERCULOSIS THREAT TO CONSERVATION AREAS AND GAME FARMS THROUGH INTRODUCTION OF UNTESTED ANIMALS	
(Hlokwe, 2011)	2011	Molecular characterisation of Mycobacterium bovis isolated from African buffaloes (Syncerus caffer) in Hluhluwe-iMfolozi Park in KwaZulu-Natal, South Africa	
(Hlokwe, 2019)	2019	First detection of Mycobacterium bovis infection in Giraffe (Giraffa camelopardalis) in the Greater Kruger National Park Complex: Role and implications	
(Hlokwe, 2014)	2014	Evidence of increasing intra and inter-species transmission of Mycobacterium bovis in South Africa: Are we losing the battle?	
(Hlokwe, 2013)	2013	Evaluation of the Discriminatory Power of Variable Number of Tandem Repeat Typing of Mycobacterium bovis Isolates from Southern Africa	
(Infantes-Lorenzo, 2019)	2019	New serological platform for detecting antibodies against Mycobacterium tuberculosis complex in European badgers	YES
(Iovane, 2020)	2020	Prevalence of serum antibodies against the Mycobacterium tuberculosis complex in wild boar in Campania region, Italy.	YES
(Jang, 2017)	2017	Isolation of Mycobacterium bovis from Free-Ranging Wildlife in South Korea	YES
(King, 2015)	2015	The variability and seasonality of the environmental reservoir of Mycobacterium bovis shed by wild European badgers	
(King, 2015b)	2015	Performance of a Noninvasive Test for Detecting Mycobacterium bovis Shedding in European Badger (Meles meles) Populations	YES
(LaHue, 2016)	2016	Spatially explicit modeling of animal tuberculosis at the wildlife-livestock interface in Ciudad Real province, Spain	
(Lambert, 2017)	2017	Host status of wild roe deer in bovine tuberculosis endemic areas	
(le Roex, 2016)	2016	Disease Control in Wildlife: Evaluating a Test and Cull Programme for Bovine Tuberculosis in African Buffalo	
(Lugton, 1998)	1998	Epidemiology and pathogenesis of Mycobacterium bovis infection of red deer (Cervus elaphus) in New Zealand	YES

(Lyashchenko, 2008)	2008	Animal-side serologic assay for rapid detection of Mycobacterium bovis infection in multiple species of free-ranging wildlife	YES
(Madeira, 2017)	2017	Factors that Influence Mycobacterium bovis Infection in Red Deer and Wild Boar in an Epidemiological Risk Area for Tuberculosis of Game Species in Portugal	YES
(Martin-Atance, 2005)	2005	Bovine tuberculosis in a free ranging red fox (Vulpes vulpes) from Donana National Park (Spain)	
(Martin-Hernando, 2007)	2007	Lesions associated with Mycobacterium tuberculosis complex infection in the European wild boar	YES
(Martino, 2017)	2017	Serology and protein electrophoresis for evidence of exposure to 12 mink pathogens in free-ranging American mink (Neovison vison) in Argentina	
(Mentaberre, 2014)	2014	Long-Term Assessment of Wild Boar Harvesting and Cattle Removal for Bovine Tuberculosis Control in Free Ranging Populations	
(Michel, 2009)	2009	Molecular epidemiology of Mycobacterium bovis isolates from free-ranging wildlife in South African game reserves	
(Miller, 2015)	2015	Antemortem Diagnosis of Mycobacterium bovis Infection in Free-ranging African Lions (Panthera leo) and Implications for Transmission	
(Miller, 2019)	2019	Fatal Tuberculosis in a Free-Ranging African Elephant and One Health Implications of Human Pathogens in Wildlife	
(Miller, 2019b)	2019	Serological reactivity to MPB83 and CFP10/ESAT-6 antigens in three suid hosts of Mycobacterium bovis infection	
(Miller, 2003)	2003	Evaluation of the influence of supplemental feeding of white-tailed deer (Odocoileus virginianus) on the prevalence of bovine tuberculosis in the Michigan wild deer population	
(Miller, 2006)	2006	Evaluation of historical factors influencing the occurrence and distribution of Mycobacterium bovis infection among wildlife in Michigan	
(Mukherjee, 2018)	2018	Isolation and analysis of the molecular epidemiology and zoonotic significance of Mycobacterium tuberculosis in domestic and wildlife ruminants from three states in India	
(Mullineaux, 2011)	2011	Managing public demand for badger rehabilitation in an area of England with endemic tuberculosis	
(Munoz-Mendoza, 2013)	2013	Wild boar tuberculosis in Iberian Atlantic Spain: a different picture from Mediterranean habitats	YES
(Nigsch, 2019)	2019	Mycobacterium caprae Infection of Red Deer in Western Austria-Optimized Use of Pathology Data to Infer Infection Dynamics	

(Norton, 2005)	2005	Ranging behaviour and duration of survival of wild brushtail possums (<i>Trichosurus vulpecula</i>) infected with <i>Mycobacterium bovis</i>	
(Nugent, 2012)	2012	Reduced spillover transmission of <i>Mycobacterium bovis</i> to feral pigs (<i>Sus scrofa</i>) following population control of brushtail possums (<i>Trichosurus vulpecula</i>)	
(Nugent, 2002)	2002	Use of released pigs as sentinels for <i>Mycobacterium bovis</i>	
(Nugent, 2016)	2016	Field Trial of an Aerially-Distributed Tuberculosis Vaccine in a Low-Density Wildlife Population of Brushtail Possums (<i>Trichosurus vulpecula</i>)	
(Obanda, 2013)	2013	First reported case of fatal tuberculosis in a wild African elephant with past human-wildlife contact	
(O'Brien, 2008)	2008	ESTIMATING THE TRUE PREVALENCE OF MYCOBACTERIUM BOVIS IN FREE-RANGING ELK IN MICHIGAN	
(O'Brien, 2002)	2002	Epidemiology of <i>Mycobacterium bovis</i> in free-ranging white-tailed deer, Michigan, USA, 1995-2000	
(Parra, 2003)	2003	Epidemiology of <i>Mycobacterium bovis</i> infections of pigs and wild boars using a molecular approach	YES
(Parra, 2006)	2006	An epidemiological evaluation of <i>Mycobacterium bovis</i> infections in wild game animals of the Spanish Mediterranean ecosystem	YES
(Pavlik, 2002)	2002	Incidence of bovine tuberculosis in wild and domestic animals other than cattle in six Central European countries during 1990-1999	
(Payne, 2013)	2013	Bovine tuberculosis in "Eurasian" badgers (<i>Meles meles</i>) in France	YES
(Pedersen, 2017)	2017	LIMITED ANTIBODY EVIDENCE OF EXPOSURE TO MYCOBACTERIUM BOVIS IN FERAL SWINE (<i>SUS SCROFA</i>) IN THE USA	
(Porphyre, 2011)	2011	Contact patterns as a risk factor for bovine tuberculosis infection in a free-living adult brushtail possum <i>Trichosurus vulpecula</i> population	
(Price-Carter, 2018)	2018	Whole Genome Sequencing for Determining the Source of <i>Mycobacterium bovis</i> Infections in Livestock Herds and Wildlife in New Zealand	
(Reveillaud, 2018)	2018	Infection of Wildlife by <i>Mycobacterium bovis</i> in France Assessment Through a National Surveillance System, Sylvatub	YES
(Richomme, 2010)	2010	Bovine Tuberculosis in Livestock and Wild Boar on the Mediterranean Island, Corsica	
(Riordan, 2011)	2011	Culling-Induced Changes in Badger (<i>Meles meles</i>) Behaviour, Social Organisation and the Epidemiology of Bovine Tuberculosis	
(Rodriguez, 2011)	2011	<i>Mycobacterium caprae</i> Infection in Livestock and Wildlife, Spain	
(Rodriguez-Campos, 2011)	2011	Limitations of Spoligotyping and Variable-Number Tandem-Repeat Typing for Molecular Tracing of <i>Mycobacterium bovis</i> in a High-Diversity Setting	

(Rodwell, 2001)	2001	Evaluation of population effects of bovine tuberculosis in free-ranging African buffalo (<i>Syncerus caffer</i>)	
(Romero, 2008)	2008	Persistence and molecular evolution of <i>Mycobacterium bovis</i> population from cattle and wildlife in Donana National Park revealed by genotype variation	YES
(Roos, 2016)	2016	Test performance of three serological assays for the detection of <i>Mycobacterium bovis</i> infection in common warthogs (<i>Phacochoerus africanus</i>)	
(Roos, 2018)	2018	Seroprevalence of <i>Mycobacterium bovis</i> infection in warthogs (<i>Phacochoerus africanus</i>) in bovine tuberculosis-endemic regions of South Africa	
(Rosenbaum, 2015)	2015	Detection of <i>Mycobacterium tuberculosis</i> Complex in New World Monkeys in Peru	
(Santos, 2015)	2015	Patterns of <i>Mycobacterium tuberculosis</i> -complex excretion and characterization of super-shedders in naturally-infected wild boar and red deer	YES
(Santos, 2009)	2009	EPIDEMIOLOGY OF MYCOBACTERIUM BOVIS INFECTION IN WILD BOAR (<i>SUS SCROFA</i>) FROM PORTUGAL	YES
(Santos, 2018)	2018	Spatial Analysis of Wildlife Tuberculosis Based on a Serologic Survey Using Dried Blood Spots, Portugal	YES
(Tomlinson, 2013)	2013	Sex-Related Heterogeneity in the Life-History Correlates of <i>Mycobacterium bovis</i> Infection in European Badgers (<i>Meles meles</i>)	
(Trcka, 2006)	2006	<i>Mycobacterial</i> infections in European wild boar (<i>Sus scrofa</i>) in the Czech Republic during the years 2002 to 2005	
(Vicente, 2013)	2013	Temporal Trend of Tuberculosis in Wild Ungulates from Mediterranean Spain	YES
(Vicente, 2019)	2019	Serum haptoglobin response in red deer naturally infected with tuberculosis	YES
(Vidal, 2006)	2006	Analysis of serum biochemical parameters in relation to <i>Mycobacterium bovis</i> infection of European wild boars (<i>Sus scrofa</i>) in Spain	YES
(Vieira-Pinto, 2011)	2011	Combined evaluation of bovine tuberculosis in wild boar (<i>Sus scrofa</i>) and red deer (<i>Cervus elaphus</i>) from Central-East Portugal	YES
(Walter, 2013)	2013	Surveillance and movements of Virginia opossum (<i>Didelphis virginiana</i>) in the bovine tuberculosis region of Michigan	
(Wanzala, 2017)	2017	Evaluation of pathogen-specific biomarkers for the diagnosis of tuberculosis in white-tailed deer (<i>Odocoileus virginianus</i>)	
(Ward, 2012)	2012	Predicting the status of wild deer as hosts of <i>Mycobacterium bovis</i> infection in Britain	
(Whipple, 1997)	1997	Restriction fragment length polymorphism analysis of <i>Mycobacterium bovis</i> isolates from captive and free-ranging animals	

(White, 1997)	1997	Fertility control as a means of controlling bovine tuberculosis in badger (<i>Meles meles</i>) populations in south-west England: predictions from a spatial stochastic simulation model	
(Wilkinson, 2004)	2004	A model of bovine tuberculosis in the badger <i>Meles meles</i> : an evaluation of different vaccination strategies	
(Winder, 2006)	2006	Metabolic fingerprints of <i>Mycobacterium bovis</i> cluster with molecular type: implications for genotype-phenotype links	
(Witmer, 2010)	2010	EPIZOOTIOLOGIC SURVEY OF MYCOBACTERIUM BOVIS IN WILDLIFE AND FARM ENVIRONMENTS IN NORTHERN MICHIGAN	
(Woodroffe, 2006)	2006	Culling and cattle controls influence tuberculosis risk for badgers	
(Woodroffe, 2005)	2005	Spatial association of <i>Mycobacterium bovis</i> infection in cattle and badgers <i>Meles meles</i>	YES
(Woodroffe, 2009)	2009	Social group size affects <i>Mycobacterium bovis</i> infection in European badgers (<i>Meles meles</i>)	
(Zanella, 2008)	2008	<i>Mycobacterium bovis</i> in wildlife in France	YES
(Zieger, 1998)	1998	Tuberculosis in Kafue lechwe (<i>Kobus leche kafuensis</i>) and in a bushbuck (<i>Tragelaphus scriptus</i>) on a game ranch in Central Province, Zambia	
(Augustynowicz-Kopec, 2011)	2011	CHARACTERISATION OF MYCOBACTERIUM BOVIS STRAINS ISOLATED FROM FARM AND WILD ANIMALS IN POLAND	
(Barasona, 2017)	2017	Environmental Presence of <i>Mycobacterium tuberculosis</i> Complex in Aggregation Points at the Wildlife/Livestock Interface	
(Barbier, 2016)	2016	First molecular detection of <i>Mycobacterium bovis</i> in environmental samples from a French region with endemic bovine tuberculosis	
(Barrow, 1981)	1981	ASPECTS OF THE EPIDEMIOLOGY OF BOVINE TUBERCULOSIS IN BADGERS AND CATTLE .2. THE DEVELOPMENT AND USE OF A TYPING SYSTEM FOR MYCOBACTERIUM-BOVIS	
(Bouchez-Zacria, 2018)	2018	The Distribution of Bovine Tuberculosis in Cattle Farms Is Linked to Cattle Trade and Badger-Mediated Contact Networks in South-Western France, 2007-2015	YES
(Bouchez-Zacria, 2017)	2017	Environmental determinants of the <i>Mycobacterium bovis</i> concomitant infection in cattle and badgers in France	
(Coleman, 2006)	2006	Trends in the incidence of tuberculosis in possums and livestock, associated with differing control intensities applied to possum populations	
(Costello, 1999)	1999	Study of restriction fragment length polymorphism analysis and spoligotyping for epidemiological investigation of <i>Mycobacterium bovis</i> infection	

(Cousins, 2003)	2003	Tuberculosis in seals caused by a novel member of the Mycobacterium tuberculosis complex: Mycobacterium pinnipedii sp nov	
(Daly, 2006)	2006	Patterns of antimicrobial susceptibility in Michigan wildlife and bovine isolates of Mycobacterium bovis	
(Doran, 2009)	2009	An outbreak of tuberculosis affecting cattle and people on an Irish dairy farm, following the consumption of raw milk	
(Erler, 2004)	2004	Molecular fingerprinting of Mycobacterium bovis subsp caprae isolates from Central Europe	
(Feizabadi, 1996)	1996	Genomic analysis of Mycobacterium bovis and other members of the Mycobacterium tuberculosis complex by isoenzyme analysis and pulsed-field gel electrophoresis	
(Griffin, 2005)	2005	Tuberculosis in cattle: the results of the four-area project	YES
(Haddad, 2001)	2001	Spoligotype diversity of Mycobacterium bovis strains isolated in France from 1979 to 2000	
(Hone, 2008)	2008	Evaluating evidence of association of bovine tuberculosis in cattle and badgers	
(Je, 2015)	2015	Extent of Mycobacterium bovis transmission among animals of dairy and beef cattle and deer farms in South Korea determined by variable-number tandem repeats typing	
(Jenkins, 2007)	2007	Effects of culling on spatial associations of Mycobacterium bovis infections in badgers and cattle	
(Katale, 2017)	2017	Isolation and Potential for Transmission of Mycobacterium bovis at Human-livestock-wildlife Interface of the Serengeti Ecosystem, Northern Tanzania	
(Krajewska-Wedzina, 2018)	2018	Molecular characterisation of Mycobacterium caprae strains isolated in Poland	
(Lavelle, 2016)	2016	Evaluating wildlife-cattle contact rates to improve the understanding of dynamics of bovine tuberculosis transmission in Michigan, USA	
(Milian-Suazo, 2008)	2008	Molecular epidemiology of Mycobacterium bovis: Usefulness in international trade	
(Moustakas, 2017)	2017	A big-data spatial, temporal and network analysis of bovine tuberculosis between wildlife (badgers) and cattle	
(Moustakas, 2015)	2015	Coupling models of cattle and farms with models of badgers for predicting the dynamics of bovine tuberculosis (TB)	
(Smith, 2011)	2011	European 1: a globally important clonal complex of Mycobacterium bovis.	
(O'Brien, 2000)	2000	Characterization of the Mycobacterium bovis restriction fragment length polymorphism DNA probe pUCD and performance comparison with standard methods	
(O'Brien, 2000b)	2000	Identification of a novel DNA probe for strain typing Mycobacterium bovis by restriction fragment length polymorphism analysis	

(OCorryCrowe, 1996)	1996	The effect of reduction in badger density on the spatial organisation and activity of badgers <i>Meles meles</i> L in relation to farms in central Ireland	YES
(Olea-Popelka, 2005)	2005	Spatial relationship between <i>Mycobacterium bovis</i> strains in cattle and badgers in four areas in Ireland	
(Olea-Popelka, 2006)	2006	Quantifying badger exposure and the risk of bovine tuberculosis for cattle herds in county Kilkenny, Ireland	YES
(Paterson, 1995)	1995	Foraging and denning patterns of brushtail possums, and their possible relationship to contact with cattle and the transmission of bovine tuberculosis	
(Pavlik, 2005)	2005	Detection of bovine and human tuberculosis in cattle and other animals in six Central European countries during the years 2000-2004	
(Perumaalla, 1996)	1996	Molecular epidemiology of <i>Mycobacterium bovis</i> in Texas and Mexico	
(Porphyre, 2007)	2007	A descriptive spatial analysis of bovine tuberculosis in intensively controlled cattle farms in New Zealand	
(Porphyre, 2008)	2008	Risk factors for bovine tuberculosis in New Zealand cattle farms and their relationship with possum control strategies	
(Prodinger, 2005)	2005	Characterization of <i>Mycobacterium caprae</i> isolates from Europe by mycobacterial interspersed repetitive unit genotyping	
(Prodinger, 2002)	2002	Infection of red deer, cattle, and humans with <i>Mycobacterium bovis</i> subsp <i>caprae</i> in western Austria	
(Ramsey, 2016)	2016	Management of on-farm risk to livestock from bovine tuberculosis in Michigan, USA, white-tailed deer: Predictions from a spatially-explicit stochastic model	
(Reilly, 2007)	2007	Husbandry practices, badger sett density and habitat composition as risk factors for transient and persistent bovine tuberculosis on UK cattle farms	
(Reis, 2020)	2020	Polyclonal infection as a new scenario in <i>Mycobacterium caprae</i> epidemiology	
(Rettinger, 2017)	2017	The Region of Difference Four is a Robust Genetic Marker for Subtyping <i>Mycobacterium caprae</i> Isolates and is Linked to Spatial Distribution of Three Subtypes	YES
(Ribeiro-Lima, 2017)	2017	Patterns of Cattle Farm Visitation by White-Tailed Deer in Relation to Risk of Disease Transmission in a Previously Infected Area with Bovine Tuberculosis in Minnesota, USA	
(Richomme, 2013)	2013	Exposure of Wild Boar to <i>Mycobacterium tuberculosis</i> Complex in France since 2000 Is Consistent with the Distribution of Bovine Tuberculosis Outbreaks in Cattle	
(Riviere, 2014)	2014	Bovine tuberculosis surveillance in cattle and free-ranging wildlife in EU Member States in 2013: A survey-based review	

(Rodriguez, 2010)	2010	High spoligotype diversity within a Mycobacterium bovis population: Clues to understanding the demography of the pathogen in Europe	
(Rodriguez, 2013)	2013	Splitting of a Prevalent Mycobacterium bovis Spoligotype by Variable-Number Tandem-Repeat Typing Reveals High Heterogeneity in an Evolving Clonal Group	
(Roring, 1998)	1998	Spacer oligotyping of Mycobacterium bovis isolates compared to typing by restriction fragment length polymorphism using PGRS, DR and IS6110 probes	
(Rodriguez-Campos, 2012)	2012	European 2--a clonal complex of Mycobacterium bovis dominant in the Iberian Peninsula.	
(Sales, 2001)	2001	Genetic diversity among Mycobacterium bovis isolates: A preliminary study of strains from animal and human sources	
(Salvador, 2019)	2019	Disease management at the wildlife-livestock interface: Using whole-genome sequencing to study the role of elk in Mycobacterium bovis transmission in Michigan, USA	
(Sauter, 1995)	1995	Behavioural studies on the potential for direct transmission of tuberculosis from feral ferrets (Mustela furo) and possums (Trichosurus vulpecula) to farmed livestock	
(Sauter, 1995b)	1995	Dominance hierarchies in cattle and red deer (Cervus elaphus): Their possible relationship to the transmission of bovine tuberculosis	
(Scantlebury, 2006)	2006	Individual trade-offs between nutrition and risk of interspecific transmission of disease by grazing: cows, badger latrines and bovine tuberculosis	
(Scantlebury, 2004)	2004	Risk of disease from wildlife reservoirs: Badgers, cattle, and bovine tuberculosis	
(Serraino, 1999)	1999	Monitoring of transmission of tuberculosis between wild boars and cattle: Genotypical analysis of strains by molecular epidemiology techniques	YES
(Sintayehu, 2017)	2017	Effect of host diversity and species assemblage composition on bovine tuberculosis (bTB) risk in Ethiopian cattle	
(Skuce, 1994)	1994	GENOMIC FINGERPRINTING OF MYCOBACTERIUM-BOVIS FROM CATTLE BY RESTRICTION-FRAGMENT-LENGTH-POLYMORPHISM ANALYSIS	
(Skuce, 1996)	1996	Differentiation of Mycobacterium bovis isolates from animals by DNA typing	
(Sleeman, 2008)	2008	Incidence of visits by badgers to farmyards in Ireland in winter	
(Smith, 2007)	2007	A cost-benefit analysis of culling badgers to control bovine tuberculosis	
(Smith, 2001)	2001	A model of bovine tuberculosis in the badger Meles meles: an evaluation of control strategies	
(Smith, 2001b)	2001	A model of bovine tuberculosis in the badger Meles meles: the inclusion of cattle and the use of a live test	
(Smith, 2012)	2012	Comparing Badger (Meles meles) Management Strategies for Reducing Tuberculosis Incidence in Cattle	

(Thomas, 2019)	2019	Validation of a new serological assay for the identification of Mycobacterium tuberculosis complex-specific antibodies in pigs and wild boar
(Trewby, 2016)	2016	Use of bacterial whole-genome sequencing to investigate local persistence and spread in bovine tuberculosis
(Triguero-Ocana, 2019)	2019	Spatio-temporal trends in the frequency of interspecific interactions between domestic and wild ungulates from Mediterranean Spain
(Tsao, 2014)	2014	Sources of bovine tuberculosis in the United States
(Vansoolingen, 1994)	1994	USE OF VARIOUS GENETIC-MARKERS IN DIFFERENTIATION OF MYCOBACTERIUM-BOVIS STRAINS FROM ANIMALS AND HUMANS AND FOR STUDYING EPIDEMIOLOGY OF BOVINE TUBERCULOSIS
(Vercauteren, 2008)	2008	Livestock protection dogs for deterring deer from cattle and feed
(Vercauteren, 2007)	2007	Fence-line contact between wild and farmed white-tailed deer in Michigan: Potential for disease transmission
(Vial, 2011)	2011	Local Cattle and Badger Populations Affect the Risk of Confirmed Tuberculosis in British Cattle Herds
(Walter, 2014)	2014	Linking Bovine Tuberculosis on Cattle Farms to White-Tailed Deer and Environmental Variables Using Bayesian Hierarchical Analysis
(Ward, 2009)	2009	ESTIMATING THE RISK OF CATTLE EXPOSURE TO TUBERCULOSIS POSED BY WILD DEER RELATIVE TO BADGERS IN ENGLAND AND WALES
(Wilber, 2019)	2019	Modelling multi-species and multi-mode contact networks: Implications for persistence of bovine tuberculosis at the wildlife-livestock interface
(Wilkinson, 2009)	2009	COST-BENEFIT ANALYSIS MODEL OF BADGER (MELES MELES) CULLING TO REDUCE CATTLE HERD TUBERCULOSIS BREAKDOWNS IN BRITAIN, WITH PARTICULAR REFERENCE TO BADGER PERTURBATION
(Woodroffe, 2009)	2009	BOVINE TUBERCULOSIS IN CATTLE AND BADGERS IN LOCALIZED CULLING AREAS
(Wright, 2015)	2015	Herd-level bovine tuberculosis risk factors: assessing the role of low-level badger population disturbance
(Zumarraga, 2013)	2013	Understanding the relationship between Mycobacterium bovis spoligotypes from cattle in Latin American Countries

1103 **Supplementary Table 2** - Discrimination of the total of events analysed by moderator.

Parameter in analysis	Total of events
Continent	
Asia	2
Europe	125
Oceania	4
Publication period	
1990-1999	7
2000-2010	33
2011-2020	91
Test	
Tuberculin-based	1
IFN-gamma	3
ELISA	11
Histopathology	57
Nucleic acid-based	4
Country	
Austria	3
France	13
Germany	5
Hungary	4
Italy	5
Ireland	6
Korea	2
New Zealand	4
Portugal	24
Spain	51
Switzerland	1
UK	14
Sample size	
<100	33
100-250	31
250-1000	34
>1000	33
Tract	
Respiratory	7
Digestive	6
Generalized	10

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1105 **Supplementary Table 3** - Discrimination of the heterogeneity of each moderator by host species, and the associated p-value obtained through
 1106 analysis of variance (ANOVA).

	Moderators	Country	Publication Period	Diagnostic Test	Sample Size	Overall		
Badger	Heterogeneity (%)	39.41	0	0	0.99	47.12		
	ANOVA p-value	< .0001	0.0557	0.0728	0.3360			
	Moderators	Continent	Country	Publication Period	Diagnostic Test	Sample Size	Tract	Overall
Red deer	Heterogeneity (%)	0	8.65	0	0	49.23	0.64	60.92
	ANOVA p-value	0.2311	0.0380	0.3520	0.3612	< .0001	0.3502	
	Moderators	Continent	Country	Publication Period	Diagnostic Test	Sample Size	Tract	Overall
Wild boar	Heterogeneity (%)	4.63	6.67	0	0	17.58	0.85	28.61
	ANOVA p-value	0.0920	0.0690	0.2872	0.7907	0.0004	0.4054	

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1109 **Supplementary Figure 1** – Retrieval and selection of articles for the review according to PRISMA

1110 guidelines.

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1112 **Supplementary Figure 2** - Publication Trends in wildlife tuberculosis.

1113 [A] Annual median rise: (a) Global (1981-2020) =5 articles per year; (b) From 2005 to 2020 = 12

1114 articles per year; [B] Number of publications according to study period (light blue; 1920-2018) and

1115 the publication year (dark blue; 1981-2020)

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1118 **Supplementary Figure 3** - Word Cloud. Top 10 most frequent words.