Global trends of epidemiological research in livestock tuberculosis for the last four decades

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Abstract

Animal tuberculosis (TB) caused by *Mycobacterium tuberculosis* complex (MTC) bacteria remains as one of the most significant infectious diseases of livestock, despite decades of eradication programs and research efforts, in an era where the livestock sector is amongst the most important and rapidly expanding commercial agricultural segments worldwide.

This work provides a global overview of the spatial and temporal trends of reported scientific knowledge of TB in livestock, aiming to gain insights into research subtopics within the animal TB epidemiology domain and to highlight territorial inequalities regarding data reporting and research outputs over the years. To deliver such information, peer-reviewed reports of TB studies in livestock were retrieved from the Web of Science and Google Scholar, systematized, and dissected. The validated dataset contained 443 occurrence observations, covering the 1981-2020 period (39 years).

We highlight a clear move towards transdisciplinary areas and the One Health approach, with a global temporal increase of publications combining livestock with wildlife and/or human components, which reflect the importance of non-prototypical hosts as key to understanding animal TB. It becomes evident that cattle is the main host across works from all continents, however many regions remain poorly surveyed. TB research in livestock in low-/middle-income countries is markedly growing, reflecting changes in animal husbandry, but also mirroring the globalization era, with a marked increase in international collaboration and capacitation programs for scientific and technological development.

This review gives an overview of the most prolific continents, countries, and research fields in animal TB epidemiology, clearly outlining knowledge gaps and key priority topics. The estimated growth trend of livestock production until 2050, particularly in Asia and Africa, in response to human population growth and animal-protein demand, will require further investment in early surveillance and adaptive research to accommodate the higher diversity of livestock species and MTC members and raising the possibility to finetune funding schemes.

1 Introduction

Tuberculosis (TB) is caused by a group of pathogenic mycobacteria grouped in the *Mycobacterium tuberculosis* complex (MTC). This is a chronic, slow-progression disease that can lead to granuloma formation, mainly in the lymph nodes and lungs (Palmer & Waters, 2006).

MTC members have been described as a series of host-adapted ecotypes, with each species or ecotype exhibiting distinct host tropism, phenotype, and pathogenicity, and marked by molecular singularities (Brites et al., 2018; Gagneux, 2018; Smith et al., 2006). *Mycobacterium tuberculosis*, *Mycobacterium africanum*, and *Mycobacterium canettii* are almost exclusively human pathogens, while the other ecotypes are animal-adapted complex members. *Mycobacterium bovis* is considered to have the widest host range: ungulates, carnivores, marsupials, rodents, lagomorphs, and primates, humans included (Rodríguez-Campos, Smith, Boniotti, & Aranaz, 2014; Thoen, Lobue, & de Kantor, 2006). *Mycobacterium caprae* was first described as main the causative agent of TB in goats (Aranaz, Cousins, Mateos, & Dominguez, 2003), however, the pathogen was already isolated from other mammal species, including wildlife and humans, mainly in European countries (Reis, Albuquerque, Botelho, & Cunha, 2020; Rodríguez et al., 2011). As for the remaining members, *Mycobacterium microti* natural hosts are rodents (Kipar et al., 2014); *Mycobacterium pinnipidii* is associated with infection in pinnipeds, such as sea lions (Cousins et al., 2003); *Mycobacterium mungi* was described in banded mongooses from Southern Africa (Alexander et al., 2010); and *Mycobacterium orygis* was originally isolated from African and Asian ungulates (van Ingen et al., 2012). Two recent additions to the MTC are still not formalized, the “chimpanzee bacillus” isolated from chimpanzee (Coscolla et al., 2013) and the “dassie bacillus” from hyrax (Mostowy, Cousins, & Behr, 2004), both in Africa.

When considering livestock animal populations, *M. bovis* and *M. caprae* are, thus far, the most relevant TB-causing agents. Indeed, several countries have implemented TB eradication programs in livestock, mainly in cattle populations, with some minor exceptions also including the test and cull of small ruminants. TB control programs are currently in progress in several European countries. Portugal, Spain, the United Kingdom, Ireland, Malta, and Italy hold such programs with co-funding by the European Union (EU, 2020). Some federal states of the United States of America (USA), New Zealand, and developing countries, that still have not achieved the TB-free status, remain incessantly working for that purpose also under test and slaughter schemes.

The livestock sector continues to evolve on a global scale, being one of the agricultural subsectors that presents a more pronounced growing rate in developing countries (Thornton, 2010). Global livestock production has increased substantially since the 1960s and is expected to grow steadily for the next decades as a consequence of the predicted increase in the demand for animal products (Thornton, 2010). It is estimated that the human population will grow, approximately, to 9 billion in 2050 and the majority will live in urban settings, two factors that, together with the shift of diets and food consumption patterns towards animal-derived protein, will contribute to the higher demand of meat supply. The rapid development of this sector can potentiate difficulties related with the control of established or emerging diseases, especially in countries with lower economic capacity to implement

surveillance and eradication programs. TB establishment in livestock causes a significant impact on several domains. First, on animal health but, being a zoonosis, also on human health. The consumption of unpasteurized dairy products and direct close contact with infected animals in the context of occupational exposure have been attributed as potential sources of infection to humans (Cvetnic et al., 2007; Kubica, Rüsch-Gerdes, & Niemann, 2003; Müller et al., 2013; Rodríguez et al., 2009). Second, it causes severe economic constraints, due to the costs associated with the implementation of surveillance or eradication programs; compensations to farmers due compulsory slaughter of reactors, the reduction in protein conversion yields and productivity; trade restrictions; and reduced value of live animals and animal-derived products.

TB in livestock is best characterized in the cattle population, however, some geographical disparities in data reporting and method standardization are evident. Moreover, despite there being national reference laboratories for diagnosis purposes in developed and developing countries which follow international guidelines from OIE, the number of research groups addressing this research topic with different resources, technical skills, and technological advancements increase the heterogeneity and quality of scientific production. A lack of comprehensive information concerning overall geographic disease prevalence, diagnostic techniques under routine application, genotyping methods, and transmission inference strategies subsist. Plus, the distribution of disease in livestock species regarded as non-prototypical for TB, such as goats, sheep, or pigs, or animals regarded as wildlife but which are highly managed and maintained in confined environments for economical purposes, such as touristic activities (e.g. dromedaries), transportation of humans and goods (e.g. llamas), game farms, zoological parks, and, others, remain poorly known on a global level. It could thus be useful to highlight the status and geographical distribution of epidemiological knowledge related to TB in livestock. Such global mapping is elemental to quickly identify trends, understand the relative contribution of livestock managing systems, spot the regions in which research dedicated to animal TB is intense or under expansion, and mark those territories that urgently need to generate new data. This systematization of knowledge may inform strategic decisions on when, where, and how should resources be allocated.

This systematic review was thus conducted with the objective to (i) illustrate the spatial and temporal distribution of scientific works addressing the epidemiological scenario of TB in livestock; (ii) evaluate the distribution of published works per different livestock hosts species and their geographic incidence; (iii) identify the reports on different members of MTC as TB agents in livestock and their relative proportion across ecotypes; (iv) evaluate the different diagnostic and differentiation methodologies that have been implemented; (v) assess the relative contribution of livestock-wildlife and livestock-human interactions in the published articles; and (vi) identify the drivers that are meaningful to TB transmission in livestock.

2 Methods

This systematic review followed the recommendations provided by the PRISMA guidelines (Fig. 1).

2.1 Data assembly

The review question was defined as “What is the current global distribution of published scientific literature of animal TB epidemiology in livestock?”. To gather the peer-reviewed database, literature searches were undertaken using a highly relevant database and search engine and the resulting articles were manually reviewed. Reports by national or international authorities concerning official data submitted by each country were not considered.

2.2 Data collection

The literature search was conducted through ISI's Web of Science online interface (<http://www.isiknowledge.com>), in all available databases, and Google Scholar (Fig. 1). 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 retrieved. The searches were last updated on 15th February 2020.

The search strategy consisted of compiling three search strings, one for each category (tuberculosis, epidemiology, and livestock), 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 “livestock”: “Livestock” OR “Farmed” OR “Cattle” OR “Sheep” OR “Ovine” OR “Goat” OR “Pig” OR “Equine” OR “Camel” OR “Dromedary” OR “Alpaca” OR “Llama”; and the intersection consisted in #1 AND #2 AND #3. The term “Farmed” was included in this search strategy to comprise all species maintained in a confined environment with human intervention, including, for example, situations of farmed game species, zoos, or animals used for touristic activities. The terms “Camel”, “Dromedary”, “Alpaca” and “Llama” were also included to consider specific production applications and touristic activities.

2.3 Inclusion and exclusion criteria

Results for all articles were imported into a bibliographic referencing tool and all query results were verified manually to exclude duplicated entries (Fig. 1). Besides, publications clearly indexed either as review, editorial, conference posters, theses, or errata were excluded (Fig. 1). Papers in languages other than English and Portuguese or inaccessible were also omitted (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 livestock, therefore articles considering experimental infection, vaccination trials or comparative and functional genomics were not included. Those articles thought to have a reasonable reflection on the review question were fully scanned and the ones not focusing on the review theme were excluded (Fig. 1 and Supplementary Table 1).

2.4 Data analysis

All publications were included 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 was performed on included articles using the Bibliometrix package in R (Aria & Cuccurullo, 2017), and the bibliometric indicators were evaluated by

176 authors, countries, sources, and thematic fields. The analyses of thematic fields were
177 performed based on “Keywords Plus”, indexing author’ keywords for the article being
178 indexed, but also indexing the terms derived from the titles of articles for those that did not
179 have author’ keywords. Additionally, all articles were fully analyzed and information
180 regarding the period of study, country of study, mammalian host, infectious agent, TB
181 transmission drivers pointed out by the authors, diagnostic and differentiation (genotyping)
182 methods, and the top five spoligotyping profiles.

183 3 Results and Discussion

184 The present study outlines the bibliometric indicators and scientific knowledge of reported
185 scientific research related to animal TB in livestock. The initial 1489 records were transferred
186 to Endnote: the duplicates ($n=46$), not relevant publications ($n=884$) [e.g. publications related
187 to *Mycobacterium avium* subsp. *paratuberculosis* or wildlife], and inaccessible publications
188 ($n=25$) were removed (Fig. 1). Additionally, incorrectly indexed reviews ($n=63$), conference
189 posters ($n=7$), and theses ($n=19$), together with other language publications ($n=1$), and
190 evidence of duplicate data ($n=1$), were excluded. After the initial screening, a total of 443
191 publications were considered (Supplementary Table 1).

192 3.1 Temporal evolution

193 This review results in the analyses of 443 documents, which originated from 115 different
194 sources, with a total of 2049 authors, published between 1981 and 2020 (39 years) with a
195 medium rise of 10 articles per year. The annual scientific production has been increasing over
196 the years since 1993, with marked growth since 2003 when the annual medium rise stands at
197 24 articles per year, reaching a peak between 2011 and 2019 (Fig. 2a). The study period (that
198 is the period of time to which animal data was related) of the analyzed documents was
199 between 1944 and 2018, with a particular increase starting in 1990, reaching a peak between
200 2004 and 2010 (Fig. 2b). Most studies reported a duration period of one to 10 years (74.3%),
201 with Oceania being the exception, wherein the majority of studies had a duration period of
202 11 to 20 years ($n=6$), while long-period studies (>20 years) were mainly performed in Europe
203 ($n=15$). The average number of citations per document was 22.32, the average number of
204 documents per author was 0.22, and the average of authors per document was 4.63.

205 These increases in studies and publications starting in 2003 could be related with the
206 European Union (EU) funding assistance to official governmental programs to control and
207 eradicate bovine TB in addition to the increasing interest of TB as a One Health paradigm
208 disease (FAO, 2011; Gibbs, 2014). The Global Fund to Fight AIDS, TB, and Malaria created
209 in 2002 (www.theglobalfund.org) raised awareness for the zoonotic potential of TB (FAO,
210 2011; Gibbs, 2014). The research agendas under the Sixth and Seventh Framework Programs
211 (2002-2013) of the EU and under the Horizon 2020 also contributed with funding to projects
212 under the animal TB or One Health umbrella. Operational programs by Member States of the
213 EU taking advantage from the European Structural and Investment Funds also applied
214 resources to the animal TB problematic during the programming period, in addition to
215 European Territorial Cooperation, cross-border or interregional operational programs. Other
216 national programs in the UK or USA, just to mention a few countries, also gave support to
217 research in animal TB epidemiology. The increase of TB research in livestock can also be
218 related with changes in animal husbandry systems and the globalization era, with a marked

increase in international capacitation programs for scientific and technological development for under-developed countries. Other specific events could also have triggered more publications, for example, the extensive badger culling program of United Kingdom implemented between 1998 and 2005 (Bourne, 2007), which, in that period and the following years, led to an increase of the number of publications at the livestock-wildlife interface; and between 2005 and 2012, the state of Minnesota in the USA implemented a series of harsh measures in white-tailed deer and cattle to re-establish the TB-free status (Cross, Heeren, Cornicelli, & Fulton, 2018), so several publications on this issue also came to light.

3.2 Geographical location

Regarding the geographic location of each publication study area, most studies were performed in Europe (number of articles=283), followed by Africa ($n=157$), South America ($n=59$), North America ($n=55$), Asia ($n=29$) and, finally, Oceania ($n=21$). Moreover, a minority of studies report study areas in more than two countries or located in different continents ($n=10$) or do not identify the study area ($n=7$). During the reviewed period, the average publication in Europe was eight articles per year, followed by four articles per year in Africa, and one article per year in the remaining continents.

Taking into consideration the institutional affiliations of all authors, authors from European and American institutions hold higher productivity, with the UK (number of publications=216), Spain ($n=207$), USA ($n=163$), Ireland ($n=118$) and Brazil ($n=103$) positioning on the top five of countries with more publications. Such score was obtained by counting the country of each author's institutional affiliations within each publication. Moreover, the UK (number of citations=2205), Spain ($n=1081$), Ireland ($n=818$), USA ($n=624$), and Australia ($n=447$) were the top five most cited countries. The lower citation of Brazilian productions may have been the result of country-specific research, with less transposition to other countries, together with some linguistic bias and limitations, since some articles were published in Portuguese and/or in national journals. In contrast, Australia showed lower production of original research papers but higher citation numbers, which could be attributed to the international interest in control and eradication measures being used in Oceania.

Regarding study location area, the UK (number of articles=68), Spain ($n=53$), Ethiopia ($n=37$), USA ($n=29$), Ireland ($n=24$), Brazil ($n=24$), and Mexico ($n=22$), were the countries that registered more than 20 articles. These countries have reported a high burden of animal TB (EFSA & ECDC, 2019; Ortiz et al., 2014; Sibhat et al., 2017), except for the USA and Brazil. Moreover, these countries stood out with high productivity in interface areas, incorporating the problematic of TB in wildlife populations and burden associated with the zoonotic potential of the etiological agent. The USA reports were limited to TB outbreaks in Minnesota and Michigan, mainly due to high contact frequencies between cattle and white-tailed deer (wildlife reservoir), but have considerable available resources to study the disease (Cross et al., 2018; Miller & Sweeney, 2013; Schmitt, O'Brien, Bruning-Fann, & Fitzgerald, 2002). Whereas Brazil reports sporadic outbreaks on a nationwide scale, but with lower overall prevalence (Neto et al., 2016).

Regarding partnerships across countries, the strong collaboration networks across European, American, and African countries are evident, with a marked number of collaborations of African and Asian emerging countries with American and European ones (Fig. 3). Alliances

between the UK and Ireland (number of collaborations=17), UK and USA ($n=14$), Spain and UK ($n=12$), Ethiopia and UK ($n=11$) and Spain and USA ($n=11$), are 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. 3). Thus, 30% of the studies in Ethiopia resulted from international collaborations with the UK, which could justify the abundance of TB studies in this African country compared to its overall scientific output. Interestingly, the works from the top 3 productive countries (UK, Spain, and USA) represent approximately 50% of international collaborations (between 45.2% (Spain) and 48.6% (USA)). This high rate of publications could also be related to the higher availability of resources to dedicate to the animal TB problematics compared to other countries. 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 60% of the top 10 of the most prolific authors.

Evaluating the affiliation of each author, the University Complutense of Madrid ($n=55$) in Spain, University College Dublin ($n=50$) in Ireland, University of Addis Ababa ($n=30$) in Ethiopia, University of Edinburgh ($n=27$) and Animal and Plant Health Agency (APHA) ($n=27$) both in the UK, and the University of Pretoria ($n=25$) in South Africa are the most highlighted institutions publishing on animal TB in livestock. The University Complutense of Madrid houses the European Union Reference Laboratory (EURL) of bovine TB in the VISAVET health surveillance center, and the APHA is an agency of the Department for Environment, Food and Rural Affairs (DEFRA) of the UK, while the other institutions are not related to official reference laboratories or agencies.

3.3 Sources

Focusing on sources, the top five publishing journals in the field of livestock TB are Preventive Veterinary Medicine (number of publications=50), followed by the Journal of Clinical Microbiology (JCM) ($n=35$), Veterinary Microbiology ($n=26$), PLOS ONE ($n=24$), and, finally, Tropical Animal Health and Production ($n=23$) (Supplementary Fig. 1). Analyzing the dynamics of these sources over the years, a predominance of the JCM is evident until 2005, when Preventive Veterinary Medicine emerged as the major publisher (Supplementary Fig. 1). This swap could be justified by the current focus of JCM on human health-related topics. Additionally, an increase over the last few years of animal TB epidemiology publications in more broad journals have been registered. However, the top five most cited sources remain the JCM (number of citations=1625), Veterinary Microbiology ($n=1010$), Preventive Veterinary Medicine ($n=805$), Veterinary Record ($n=472$), and PLOS ONE ($n=348$). So, despite not being one of the top publishers, the works published by Veterinary Record on livestock TB can be perceived as of high interest in this scientific field.

To study the temporal evolution of fields of publication among the 443 publications, 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 2005 (Fig. 4). “Infectious diseases” is the main emergent publication field since 2011, contrary to “Microbiology” that has been decreasing in the last few years (Fig. 4). “Science and Technology – Other Topics” is also emergent due to an increase of reports in more generalized journals, such as PLOS ONE (Fig. 4). Thus, an increasing tendency of authors

to publish in journals more related to infectious diseases, instead of general microbiology, can be perceived and, at the same time, an aptitude to publish in more global, open access, publications, in parallel with increased interest of the general scientific community in animal TB, whereas earlier publications were more restricted to researchers with academic degrees in veterinary medicine.

The top five more *globally cited* papers retrieved (i.e., the number of times an article that integrates the collection has been cited by any other article) are the Nature letter by Gilbert *et al.* (2005) (number of citations=234), one of the first reports describing large temporal and spatial data on cattle movements and their relationship with bovine TB epidemiology in Great Britain (Gilbert *et al.*, 2005); the article reporting the use of spoligotyping as a tool for *M. bovis* differentiation by Aranaz *et al.* (1996) ($n=189$) that is maintained nowadays as the gold-standard method for MTC strains genotyping and molecular epidemiology studies (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) ($n=131$) that was used for several years as the gold-standard for genotyping of MTC isolates, including *M. bovis* (van Soolingen, de Haas, Hermans, & van Embden, 1994); and the article by Smith *et al.* (2003) ($n=126$) reporting the clonal expansion of *M. bovis* in Great Britain, essential for the assembly of predictive evolutionary scenarios that have been produced ever since (Smith *et al.*, 2003).

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 in 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=58) (Aranaz *et al.*, 1996); the article by Haddad *et al.* (2001), regarding spoligotype diversity in French isolates ($n=50$) (Haddad *et al.*, 2001); the article by Gilbert *et al.* (2005), describing the interactions between cattle movements and bovine TB in Great Britain ($n=36$) (Gilbert *et al.*, 2005); an article evaluating MIRU-VNTR epidemiological relevance and establishing the comparison with RFLP by Allix *et al.* (2006) ($n=33$) (Allix *et al.*, 2006); and finally, the article describing the spoligotype diversity of *M. bovis* and *M. caprae* strains isolated from different animals in Portugal by Duarte *et al.* (2008) ($n=31$) (Duarte, Domingos, Amado, & Botelho, 2008).

This panel of papers reflects the generalized interest of the scientific community in obtaining a deeper knowledge of MTC members' population structure and diversity and to go on building hypothetical transmission networks.

Two clusters result from the co-citation network analysis built on global citation data (i.e. the full set of references cited by the analyzed papers), which put (Kamerbeek *et al.*, 1997) and (Cosivi *et al.*, 1998) as the central articles of each of these clusters (Supplementary Fig. 2). The first cluster comprises several articles approaching different aspects of mycobacterial molecular evolution, including MIRU-VNTR method description (Frothingham & Meeker-O'Connell, 1998), the evolutionary scenario of MTC (Brosch *et al.*, 2002), as well as the phylogeography of the *M. bovis* clonal complexes (Smith, 2012), among others (Supplementary fig. 2). The latter cluster is mainly composed of review articles about the different aspects of epidemiology and transmission of MTC, particularly *M. bovis* (e.g. (Ayele *et al.*, 2004; Corner, 2006; Humblet, Boschioli, & Saegerman, 2009)) (Supplementary Fig. 2).

3.4 Thematic

The top 10 most frequently found terms in Keywords Plus were “epidemiology” (number of occurrences=163), “*Mycobacterium bovis*” ($n=130$), “cattle” ($n=122$), “infection” ($n=121$), “transmission” ($n=87$), “diagnostic” ($n=80$), “tuberculosis” ($n=77$), “differentiation” ($n=62$), “animals” ($n=58$), and “identification” ($n=55$) (Supplementary Fig. 3). The words match the focus of the research on the transmission and epidemiology of animal TB in livestock, however, it is perceivable that most works are based on the diagnostic of animal TB, followed by the differentiation (genotyping, to be more accurate) and, finally, the identification of MTC strains. Additionally, the co-occurrence network analysis of Keyword Plus resulted in the establishment of two clusters, one composed by words related to molecular epidemiology, such as identification and differentiation (i.e. genotyping) of MTC strains, while the other cluster is composed of words related to disease transmission risk factors and diagnosis.

According to the description of samples from wildlife and/or human origin in association with samples from livestock, the articles were divided into four groups: livestock, livestock-wildlife, livestock-human, or livestock-wildlife-human. The majority were exclusively livestock-related (64.1%), followed by the livestock-wildlife components (23.5%), livestock-human interface (8.6%), and, finally, highlighting the One Health perspective at the interfaces of livestock, wildlife, and humans (3.8%). In this assessment, both the livestock-wildlife interface and the zoonosis-related studies have been increasing since 2004, coupled with the increasing number of cattle-related studies, contributing to global expansion in animal TB-related studies (Fig. 5a). A clear accumulation in the publication rate of studies focusing on the interface between livestock and wildlife, of 3 articles per year, was registered.

Livestock-specific studies are the most reported across all continents (ranging from 42% in North America to 7% in Asia), except the Oceania continent where livestock is usually studied together with the wildlife (45.0%) or with wildlife and human components (45.0%) (Fig. 5b). Studies focusing on the livestock-wildlife interface were also mainly conducted in Europe (40.6%) (Fig. 5b). In these two continents, since the end of the 20th century, the acknowledgment of wildlife TB reservoirs has been consolidated (Cooke, Jackson, Coleman, & Alley, 1995; Gallagher, Monies, Gavier-Widen, & Rule, 1998) and animal TB became most frequently tackled from the multi-host, wildlife-livestock, perspective, progressively driving more interface studies, while the addition of the One Health perspective led to the inclusion of humans into the equation (FAO, 2011; Gibbs, 2014). However, the majority of studies focusing on the zoonotic potential of animal TB remain in Africa (18.3%) and North America (15.3%) (Fig. 5b). Africa seems to be the continent where the zoonotic and reverse zoonotic (i.e. zooanthroponotic) dimensions of TB appear more frequently as a concern, together with North America. While socioeconomic and cultural factors are evident for Africa prominence on this subject, given the great physical proximity and interaction of humans with animals, the reasons behind North America centering on the zoonotic component are related to the origin of many studies from Mexico. In African countries, and to a lesser extent, in Mexico, livestock production is mainly based on small farms, where often the animals are kept near their owners, with the additional problem of raw milk and raw milk-derived product consumption (Carruth et al., 2016). These factors increase the risk of exposure to TB both in the cases of zoonosis and reverse zoonosis.

3.5 Diagnostic and genotyping methodologies

The analysis of the most frequent diagnostic and genotyping methods within the publication dataset scrutinized in this review was conducted. In the first group, histopathology (32.4%), tuberculin-based diagnosis (29.8%) and nucleic acid-based methods (24.6%) were the most prevalent (Fig. 6a). Furthermore, about half of works included a bacteriological isolation step in their workflow, and when consider nucleic acid and biochemical identification methods, culture was performed as prior step in over 90% of works. Bacteriological culture and histopathology diagnosis remain the reference methodologies to confirm a diagnosis for animal TB *in vitro* (OIE, 2018), this high occurrence was expected. Tuberculin-based diagnosis is the most used method for *in vivo* diagnosis, due to its low cost-benefit, and the recognition by the OIE and the European Commission of this method as a primary screening test for the *ante mortem* diagnosis of TB in cattle, which also contributes for its higher applicability (OIE, 2018). The ratio between the three major diagnostic methods is similar across continents, with three exceptions: Oceania reported more tuberculin-based studies (41.7%) and less nucleic acid-based (16.7%); South America performed more nucleic acid-based studies (34.6%) and less tuberculin-based ones (17.3%); and Asia performed less histopathology-based works (22.4%) (Fig. 6a). Interferon-gamma test was developed in 1990, however, it is still a rarely used method for a diagnosis of animal TB (4.3%), with no studies reported in Asia, due to its high cost, complexity, and need to process blood samples for the laboratory sensitization test within a few hours, being mainly used as an ancillary assay to clarify uncertain tuberculin test results and to give laboratory assistance to chronically infected herds. But it is not planned in control and eradication programs as a first-line diagnosis method (OIE, 2018) (Fig. 6a). Biochemical assays to identify MTC members are not commonly reported (8.9%), once they have been replaced over the years by nucleic acid-based identification methods.

In the second group, spoligotyping is the gold-standard method for genotyping of MTC isolates, followed by MIRU-VNTR (Haddad, Masselot, & Durand, 2004). Since the publications of spoligotyping in 1997 and MIRU-VNTR in 2006, both have been increasingly used, reaching a similar number of occurrences in the last years (57.9% and 42.1%, respectively), indicating an increased combination of both approaches, a trend that is observed across all continents (Fig. 6b).

More recently, since 2012, studies started to implement whole-genome sequencing (WGS) analyses ($n=20$), mainly in Europe ($n=7$) and North America ($n=6$), to differentiate at a fine-scale MTC isolates and to try to infer epidemiological relationships (e.g. (Lasserre et al., 2018; Orloski et al., 2018; Price-Carter et al., 2018)).

Additionally, studies using network-based analyses have progressively been implemented in the animal TB field ($n=49$ publications), in particular in Europe ($n=29$), highlighting the scientific recognition of the importance of animal movement, animal interactions, and disease epidemiology, in several TB settings and scenarios.

Finally, works concerning epidemiological models ($n=80$ publications) have progressively accumulated in the past two decades, being Europe ($n=58$) the continent with most publications. The awareness of animal TB complexity, and the notion that different variables impact different disease settings, evidenced the necessity of developing transmission models, to inform control actions.

3.6 Hosts

Most studies reported animal TB in farmed animals (90.4%), followed by infection in zoo animals (6.7%) and pets (2.9%). Most of the farmed animals retrieved in the publications belonged to the Bovidae family (82.1%), followed by Suidae (6.7%), Cervidae (6.2%), Camelidae (3.5%) and other (1.5%). The category denominated as “other” included a diverse range of host species, such as horse, broiler, lynx, donkey, and rabbit. Dogs, cats, rabbits, and ferrets were included in pets; while the zoo category encompassed over 20 different hosts, including elephants, giraffe, sea lion, or rhinoceros. Cattle was the most represented within the Bovidae family (82.3%), followed by small ruminants (12.3%), such as goat, sheep, and mouflon, and, finally, buffalo (3.6%) and bison (1.8%). The publication rate related to infection in farmed animals increased by 14 articles per year, while reports of infection in zoo and pet animals only started in 1994 and have had an increase of one article per year. Infection in Bovidae members has been reported with an increase of 11 articles per year, while the other families of farmed animals showed an increase of one article per year. Cattle-related articles showed an increase in publication rate of nine articles per year, followed by two articles per year in small ruminants, while works in the remaining groups of the Bovidae family show stagnation in publication. Europe was the continent where studies regarding zoo (number of studies=23) and pet ($n=9$) animals were predominant.

Depending on the region of the world, cattle and buffalo are two important livestock species, bred and maintained for meat and milk purposes, and also as a draft power source. Cattle are widespread across the world, presenting highest densities in Asia (more specifically, in India, where such animals are not slaughtered), in Eastern African countries (particularly, Ethiopia), in Northern Europe and South America, while buffalos are concentrated in Asia, mostly in India and China (Gilbert et al., 2018; Robinson et al., 2014). The predominance of cattle as a host species in the set of retrieved publications, with works across all continents, was expected, not only by the prototypical association as an *M. bovis* reservoir but also because of its global distribution and economical relevance.

The small ruminant population includes goats and sheep that have distinctive global distributions, with the majority of works having origin in Europe ($n=39$). The higher densities of goats were located in Asia (particularly, in India) and Africa, whereas the higher densities of sheep were found in Europe, central Africa, and Asia (Gilbert et al., 2018). The absence of studies concerning these hosts in South and North America might be related to less active production systems and, probably, with the allocation of research resources to other species with higher economic value. Only two studies in small ruminants originated from Asia, a vast geographic location with higher animal density than the rest of the world. So, it becomes evident that more research is a need in this geographical region and that research resources should be instigated in this field.

Studies related to Suidae members (including wild boar) were mainly performed in Europe ($n=25$), followed by Africa ($n=6$) and Oceania ($n=3$). This asymmetrical distribution might be related with the global distribution of pig production systems, that is influenced by religious and cultural factors, with few occurring in predominantly Islamic countries and with higher density in East Asian (particularly, China), Eastern Pacific countries, and European countries (Gilbert et al., 2018; Robinson et al., 2014). Despite the high density of pig production systems in Asia, there is an absence of information concerning animal TB, so it could also be a relevant topic of research for this continent. Moreover, farmed wild boar, from the Suidae family, was also referred in European studies, but to a much lesser extent

($n=6$). This species is often maintained in fenced areas (game farms) in several Western Mediterranean countries, such as Spain and France, where it is an important game species.

The Cervidae family has mainly been studied in Europe ($n=16$) and North America ($n=14$), which could also be associated with the occurrence of deer farms developed for meat production or hunting purposes.

Camelidae have only been studied in Europe ($n=11$) and Africa ($n=8$). Currently, these species are used for meat, milk, and hair fiber production and are distributed across South America, Northern Africa, East Europe, East Asia, and Australia, also being very popular as pet and zoo animals in Europe and North America (Zarrin et al., 2020), and for touristic purposes in the Canary Islands and Morocco. Climate change and the transformation of environments towards arid conditions might change the importance of this species in the production systems (Zarrin et al., 2020), therefore TB in camelids could be an important field of research in the future.

3.7 Infectious agents

The retrieved publications reported infection by seven MTC species or ecotypes: *M. bovis* (76.8%), *M. caprae* (9.1%), *M. tuberculosis* (8.9%), *M. pinnipedii* (2.5%), *M. africanum* (1.4%), *M. microti* (0.9%), and *M. orygis* (0.5%). An increase in publication rate of 9 articles per year related with *M. bovis* studies and of 1 article per year for *M. tuberculosis*- and *M. caprae*-related works were observed. The increasing number of publications reporting infection with *M. tuberculosis* in livestock animals is probably related to an augmented interest at the livestock-human interface, namely reverse zoonosis (e.g. (Adesokan et al., 2019; Mittal et al., 2014; Prasad et al., 2005)). On the other hand, the increased number of publications reporting livestock infection with *M. caprae* is probably related with the recent recognition of *M. caprae* as a separate species from *M. bovis* (Aranaz et al., 2003), together with the increasing interest in livestock members other than cattle (e.g. goats are referred as *M. caprae* main hosts (Rodríguez et al., 2011)).

The above-mentioned MTC species were predominant in farmed animals, except for *M. pinnipedii* that was mostly reported in zoo animals ($n=10$), while only *M. bovis* has been reported in pets. Reports on *M. microti* and *M. africanum* were restricted to farmed animals, with the former being mainly registered in Camelidae members ($n=3$) and the latter exclusive of cattle ($n=6$). All other MTC species were predominantly found in Bovidae members. Published works on Cervidae members were limited to *M. bovis* infection. Except for *M. microti*, the remaining MTC species were more prevalent in cattle. *M. bovis* was the most prevalent MTC species across all Bovidae members.

M. bovis was the most reported infectious agent across all continents, whereas *M. orygis* was exclusively reported in Asia and *M. africanum* in Africa. *M. bovis*, *M. caprae*, *M. microti*, and *M. pinnipedii* were predominant in Europe, while *M. tuberculosis* was predominant in Africa.

In the articles using spoligotyping as a genotyping technique, the top 5 most prevalent profiles within each MTC ecotype were registered, per article, and analyzed. *M. bovis* was predominantly identified as SB0121 (10.2% of articles) and SB0120 (7.3%), *M. caprae* as SB0157 (19.5%) and SB0418 (19.5%), and *M. tuberculosis* as SIT53 (20.0%) and SIT149 (11.4%). *M. microti*, *M. orygis*, and *M. pinnipedii* spoligotypes were only registered once:

SB0118, SIT587, and SB1162, respectively. The extensive information regarding *M. bovis* also allowed performing geographic stratification by continent. SB0140 (18.2%) was the most prevalent in Asia, SB0133 (6.7%) and SB0944 (6.7%) were equally recorded in Africa, SB0121 (15.9%) and SB0120 (9.0%) were the most frequently found in Europe, SB0673 (16.3%) and SB0145 (14.3%) were the most reported from North America, and SB0140 (14.3%) and SB0121 (12.9%) were the most stated in South America. Regarding Oceania, only four spoligotypes were registered, all with the same prevalence (25%): SB0130, SB0140, SB1031, and SB1504. These results support the geographic stratification of molecular types across continents, possibly related to trade relationships and historical grounds, namely the colonial history of many former European colonial empires that fomented animal movement across colonies and territories.

3.8 Disease transmission drivers

The transmission drivers of animal TB most frequently mentioned by the authors of selected publications were analyzed. Management strategies (25.3%) and livestock-wildlife interactions (22.3%) were the most predominant studied drivers, followed by disease agents (19.2%) and host features (18.5%) (Fig.7). Management strategies include factors such as herd structure, herd type, or cohabitation of different species; the disease agent category considers differential prevalence of infection associated with different MTC members and with different MTC strains; and host features include sex, age, breed, or body condition as some of the considered aspects. Animal movements (5.8%), livestock-human interactions (5.6%), and environmental characteristics (3.3%) also came to light (Fig. 7).

In Europe and Oceania, livestock-wildlife interactions (27.9% and 42.1%), management strategies (27.4% and 26.3%), and the disease agent (19.3% and 26.3%) were the main drivers of transmission of animal TB. In Africa and North America, host features (35.5% and 20.0%) and management strategies (22.7% and 25.7%) were reported as being the most predominant (Fig. 7). In Asia, both host features (42.1%) and disease agent (26.3%) were the most referred drivers, while in South America, disease agents (36.4%), management strategies (27.3%), and livestock-human interactions (22.7%) were the major drivers (Fig. 7).

In agreement with these perceptions and results, control and eradication programs of animal TB in most countries have as main targets the improvement of management strategies, such as biosecurity measures and herd-related features, and restriction to livestock-wildlife interactions by fencing and application of selective feeders that allow the access to food by one species, but restrict the access to a different species, due to the feeder design (Pereira, Reis, Ramos, & Cunha, 2020). However, the disease agent, such as different MTC species and the underlying genetic heterogeneity of ecotypes, as well as host features, such as sex, age, and breed, are more difficult parameters to control in the field, with the agent being almost impossible to control and the host being, nowadays, controlled through genetic selection, by the increased exploitation of animal breeds more resistant to animal TB (Pereira et al., 2020). However, this genetic selection is still rarely applied and the real effect of genetics in animal TB resistance is still poorly understood and profited.

3.9 Overview

As global human population is expected to increase from approximately 7.8 billion in 2020 (worldometers.info, 2020) to approximately 9.2 billion by 2050 (UNDP, 2008), demands for animal-based protein have driven the implementation of more industrialized methods of animal-food production, leading to an increase of intensive husbandry with subsequent effects on the transmission of infectious agents. Industrial systems for livestock production are now characterized by large numbers of animals being raised mainly in confinement, with the goal of rapid population turnover at a single infrastructure/site.

With the unceasing rise of the human population, livestock production industry will need to evolve to quickly respond to demand, with predictions estimating that production probably will need to increase by 70% until 2050 (Derner et al., 2017) and that the request for livestock products will be largely concentrated in Asia, Africa, and South America.

From 1968 until 2018, cattle production globally increased 29% and sheep by 22%, while the population of goat, pig, and buffalo duplicated. Estimates are that these numbers will keep on growing until 2050 (Derner et al., 2017; FAO, 2020). However, these trends are not constant throughout the globe: Africa and Asia registered an increase in cattle, sheep, and goat populations, whilst pig production rose in Africa and buffalo in Asia. In Europe, North America, and Oceania, the opposite situation occurred, with a reduction or stagnation of the total population of different animal species (Derner et al., 2017; FAO, 2020). Although it is still kept at high levels, meat production has reached a plateau in high-income countries since the 2000s but it has grown by 68%, 64%, and 40% in Africa, Asia, and South America, respectively. Growth in low- and middle-income countries is largely attributed to the transition to high-protein diets and, to a lesser extent, the increase of the human population in those regions.

On average and on a global level, estimated livestock losses due to infectious disease represent more than 20% of total losses (Derner et al., 2017), and since, in the future, infectious diseases will remain dynamic, the implemented surveillance system will need to be flexible and easily adapt to the incoming challenges (Derner et al., 2017). Furthermore, stakeholders will have to become aware of the benefits from risk-based approaches to early detection surveillance and by implementing effective strategies to improve farmer awareness and engagement with veterinary health services.

The expected differential growth between developed and developing countries carry different challenges to livestock production systems. In developed countries, many production systems are increasing their efficiency and environmental sustainability, such as a reduction in greenhouse gas emissions, while in developing countries the rapidly increasing demand for livestock products is favoring the intensification of production systems. The exponential growth of livestock production systems focusing on particular species and the increasing importance of others, like camelids, give an important opportunity to improve knowledge of animal TB epidemiology in hosts other than cattle, where information is scarce from continents other than Europe. Since livestock production will need to rapidly increase in Africa, Asia, and South America to accompany the population growth and the underlying animal-protein demand, these geographic locations that currently mostly support works on cattle might need to extend their fields of research, perhaps promoting international collaborations with countries with more experience in other hosts and epidemiological scenarios.

3.10 Limitations

Several limitations related to the strategy to acquire information on the published works are acknowledged. Firstly, the use of Web of Science and Google Scholar to recover the academic literature implied the exclusion of all grey literature, such as books and reports. Secondly, the use of topic, in the Web of Science, and title, in Google Scholar, as a section to search, limited the indexation of literature not including the search terms in those sections. Thirdly, the restriction to English and Portuguese articles leads to a linguistic bias, excluding valid literature produced in other languages. Additionally, it is important to highlight that 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 do not imply any value judgment for the quality or relevance of a particular study, author, institution or publication. We thus highlight that there are many meaningful and relevant publications and authors that could not be ranked according to the established criteria.

Also, given the wide broad scope of research works in animal TB, instead of focusing all the themes that gravitate around this disease, we opted to focus on a subset of topics related with the epidemiological component of TB. This strategy and the underlying criteria will of course not highlight nor cite all golden papers and renowned scientists working on animal TB.

Having mentioned these constraints, we believe that our findings offer a valid representation of research outputs within this research field at a global level.

4 Conclusions

This study provides an overview of animal TB epidemiology research in livestock on a worldwide scale, reporting valuable information related to publication numbers, countries, sources, mammalian hosts, infectious agents, and drivers of transmission. During the four decades under study, several advances in trends and knowledge occurred. The obtained data show a general growth of this field of research, mainly reflected in the increase of scientific production and international collaboration across European and American countries. The literature is strongly based on European countries, performing short period studies (<10 years) on cattle infected with *M. bovis*. Apart from this dominance of studies from Europe as a whole, countries on the top 10 are grounded on Europe, Africa, and America (both North and South), reflecting the strong international collaboration network among those continents. Additionally, an increasing tendency of authors to publish in more global journals was detected, reflecting an increased interest of the scientific community in general for animal TB epidemiology. Moreover, a progressive increase in both livestock-wildlife interface and zoonosis-related publications was noticed, with both Oceania and Europe being more aware of, or better equipped to lead with, the importance of wildlife reservoirs in animal TB epidemiology and the One Health perspective. Studies from Africa focus on zoonosis and zoonanthroponosis (reverse zoonotic disease transmission) components due to the poor livestock farming conditions and non-pasteurized milk. Furthermore, tuberculin-based methods, histopathology and nucleic acid-based methods were the more prevalent diagnosis tools, while spoligotyping and MIRU-VNTR were the most prevalent genotyping tools. An increase in both WGS and network analysis has occurred in the last few years, being an expected trend for the next decade, which may justify a literature reappraisal in the coming years. Finally, management strategies and livestock-wildlife interactions were the most

predominant identified transmission drivers. This review shows the value of bibliometric methods to illustrate global research trends of animal TB epidemiology in livestock, providing a useful reference for academics, veterinarians, funders, and policy decision-makers in the past and emerging subtopics within animal TB.

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6 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be perceived as a potential conflict of interest.

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 redirected all drafts. All authors gave intellectual input to the conceptualization 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.

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Figure captions

Figure 1 – Retrieval and selection of articles for the review according to PRISMA guidelines.

Figure 2 - Trends in publication on tuberculosis in livestock.

[A] Annual median rise: (i) Global (1981-2020) = 10 articles per year; (ii) From 2003 to 2020 = 24 articles per year; [B] Number of publications according to the study period (black 1944-2018) and the publication year (grey; 1981-2020).

Figure 3 – 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 thicker lines.

Figure 4 – Trends in sources' field over time.

Figure 5 – Interface analyses. [A] Number of publications according to interface type over time; [B] Percentage of publications according to interface type per continent.

Figure 6 – Trends in methodologies per continent. [A] Nucleic acid-based testing; Biochemical testing; Histopathology; IFN-gamma testing; Tuberculin-based testing. [B] Spoligotyping and MIRU-VNTR typing.

Figure 7 – Drivers of tuberculosis in livestock per continent.

Figure 1

Figure 2

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Figure 5

Figure 6

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