microorganisms

MDPI

Review

Evidence, Challenges, and Knowledge Gaps Regarding Latent Tuberculosis in Animals

Pamela Ncube, Bahareh Bagheri, Wynand Johan Goosen, Michele Ann Miller and Samantha Leigh Sampson *

DSI/NRF Centre of Excellence for Biomedical Tuberculosis Research, South African Medical Research Council Centre for Tuberculosis Research, Department of Biomedical Sciences, Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University, Francie Van Zijl Dr, Parow, Cape Town 7505, South Africa

* Correspondence: ssampson@sun.ac.za; Tel.: +27-21-938-9951

Abstract: *Mycobacterium bovis* and other *Mycobacterium tuberculosis* complex (MTBC) pathogens that cause domestic animal and wildlife tuberculosis have received considerably less attention than *M. tuberculosis*, the primary cause of human tuberculosis (TB). Human TB studies have shown that different stages of infection can exist, driven by host–pathogen interactions. This results in the emergence of heterogeneous subpopulations of mycobacteria in different phenotypic states, which range from actively replicating (AR) cells to viable but slowly or non-replicating (VBNR), viable but non-culturable (VBNC), and dormant mycobacteria. The VBNR, VBNC, and dormant subpopulations are believed to underlie latent tuberculosis (LTB) in humans; however, it is unclear if a similar phenomenon could be happening in animals. This review discusses the evidence, challenges, and knowledge gaps regarding LTB in animals, and possible host–pathogen differences in the MTBC strains *M. tuberculosis* and *M. bovis* during infection. We further consider models that might be adapted from human TB research to investigate how the different phenotypic states of bacteria could influence TB stages in animals. In addition, we explore potential host biomarkers and mycobacterial changes in the DosR regulon, transcriptional sigma factors, and resuscitation-promoting factors that may influence the development of LTB.

Keywords: animal tuberculosis; domestic animals; host–pathogen interactions; latent tuberculosis; *Mycobacterium bovis*; *Mycobacterium tuberculosis*; persister bacilli; phenotypic states; wildlife tuberculosis

Citation: Ncube, P.; Bagheri, B.; Goosen, W.J.; Miller, M.A.; Sampson, S.L. Evidence, Challenges, and Knowledge Gaps Regarding Latent Tuberculosis in Animals. *Microorganisms* **2022**, *10*, 1845. https://doi.org/10.3390/microorganisms10091845

Academic Editor: Radovan Václav

Received: 12 August 2022
Accepted: 9 September 2022
Published: 15 September 2022

1. Introduction

Tuberculosis is a global threat to animals and humans. In 2020, there were 1.4 million human TB deaths [1]. Although precise numbers are unknown, an estimated 1%–15% of human TB cases are believed to be zoonotic, with transmission originating from animals [2–4]. Generally, *M. tuberculosis* infection causes human TB [5], with *M. bovis* the most common infectious agent contributing to animal TB (Table 1) [6]. A wide range of domestic animals (e.g., cattle, goats, sheep, pigs) [7–10] and wildlife (e.g., buffaloes, elephants, lions, wild dogs, warthogs) [6,11,12] can be infected by *M. bovis* and other *M. tuberculosis* complex (MTBC) species including *Mycobacterium caprae*, *Mycobacterium canettii*, *Mycobacterium pinnipedii*, *Mycobacterium mungi*, *Mycobacterium africanum*, *Mycobacterium suricattae*, *Mycobacterium microti*, *Mycobacterium orygis*, the "chimpanzee bacillus", and the "dassie bacillus" (Table 1) [13–16]. Animals with TB can be a source of infection to other animals and humans [17,18]. Given the zoonotic potential and the detrimental effect that TB can have on humans and animals at human–animal–environment interfaces [19], it is important to develop an understanding of TB pathogenesis during different stages of *M. bovis* infection in animals in order to improve control and management strategies.

While there is increased recognition of the complexity of TB stages of infection in humans [20] and animals [21,22], limited studies define the characteristics and diagnosis of these stages in naturally infected animals [21,23–25]. The identification of animals that

are TB test-positive based on immunological responses [e.g., tuberculin skin test (TST) or interferon-gamma (IFN-γ) release assay (IGRA)] but lack visible lesions on necropsy or are mycobacterial culture-negative, has led to a debate on whether animals can develop LTB [24–27]. Host-(e.g., genetic variation, immunocompetence, comorbidities) [1,28] and pathogen-specific (e.g., MTBC strains, virulence, infecting dose) [29–31] factors likely impact the outcome of infection. However, it is unclear whether these stages in animals mimic those observed in humans, and this requires additional research [32].

One global challenge is that current animal TB control programs in many countries require the culling of any suspected infected animal to prevent its spread [33–35]. The culling of TB test-positive animals or depopulation of a herd is usually performed without clear knowledge of the animal's infection stage; this can lead to unnecessary loss of latently infected animals that are not shedding [36–38]. Culling animals has significant negative economic implications for animal owners. Similarly, the removal of wildlife can have negative conservation impacts, including loss of genetic diversity for some high-value species, such as rhinoceros [39,40]. It is also important to consider the implications of latent infection in livestock destined for consumption [18,41–43] and wildlife such as buffaloes or lions (which are maintenance hosts) [44–46]. In addition, the diagnosis of TB can lead to movement restrictions [40], resulting in financial losses from game sales, hunting, and ecotourism [47]. Therefore, there is a crucial need to improve the understanding of animal TB pathogenesis, infection stages, and epidemiology to inform disease control and management strategies.

Knowledge gaps still exist regarding infection stages in animal TB, as well as host–pathogen interactions and the pathogen metabolic processes involved [48]. Although research on TB diagnosis in different species has progressed [12], studies on TB pathogenesis are complicated by the lack of clinical signs in animals until the disease is advanced, which can take months to years [6,49]. Additionally, TB in wildlife may only be detected while conducting postmortem examinations [50]. Cases with early or subclinical infection can be easily missed without a thorough examination [51], especially during abattoir inspection or field necropsy [52]. These challenges have delayed progress in research on the pathogenesis and elucidation of different infection stages in animals.

The importance of understanding the stages of TB infection in animals stems from the impact it has on the diagnosis and management of infection in individuals as well as intra- and inter-species transmission risk [53]. In turn, this can inform disease control strategies in domestic and wild animals, which affects livelihoods, food security, and conservation [2,39,54]. This review describes the current state of latent TB research in domestic and wild animals and the challenges that still hinder this area of investigation. Specifically, there is a focus on understanding how different hosts (humans vs. domestic animals vs. wildlife) vary in the progression of infection, mycobacterial metabolic activity/pathways that may underly latent TB, and the influence of host–pathogen interactions. Further, we discuss the challenges that exist with TB diagnostic tools in animals. By identifying the knowledge gaps surrounding the progression of TB infection in animals, future investigations can target translational research on animal TB management and control strategies, especially for endangered wildlife and species with high commercial value. This would protect the livelihoods of domestic farmers, especially in developing countries, so as to mitigate TB disease and potential zoonotic outbreaks at human–domestic animal–wildlife interfaces.

Table 1. *Mycobacterium tuberculosis* complex pathogens and their hosts.

MTBC Pathogens	Primary Hosts	Secondary/Sporadic Hosts
M. bovis	African buffaloes (*Syncerus caffer*) [44,55,56], Asian elephants (*Elephas maximus*) [57–62], bushbucks (*Tragelaphus scriptus*) [28,63,64], bush pigs [40,65,66] (*Potamochoerus porcus*), cattle [18,67–69], chacma baboons (*Papio ursinus*) [28,70,71], cheetahs (*Acinonyx jubatus*) [70,72], common duiker (*Syvicapra grimmia*) [12,73], African elephants (*Loxodonta africana*) [28,59,74], eland (*Taurotragus oryx*) [28,40,66], giraffe (*Giraffa camelopardalis*) [75], european badger (*Meles meles*) [76–79], honey badger (*Mellivora capensis*) [12,28,80], greater kudu (*Tragelaphus strepsiceros*) [72,81], hippopotamus (*Hippopotamus amphibius*) [82,83], impala (*Aepyceros melampus*) [28,40,84], African leopards (Panthera pardus) [28,35,85], African lions (*Panthera leo*) [6,11,28,86–89], banded mongoose (*Mungos mungo*) [90,91], nyala (*Tragelaphus angasii*) [28,92] black rhinoceros (*Diceros bicornis*) [6,93–95], red fox (*Vulpes vulpes*) [96], spotted genet (*Genetta tigrine*) [28,65,81], springbok (*Antidorcas marsupialis*) [12,28], common warthog (*Phacochoerus africanus*) [28,97–99], wild boars (*Sus scrofa*) [96], African wild dog (*Lycaon pictus*) [100–103], blue wildebeest (*Connochaetes taurinus*) [104,105], wild deer (*Capreolus capreolus*, *Cervus elaphus*) [96], white rhinoceros (*Ceratotherium simum*) [35,95,104,106]	Humans [17,19,43], cats [107]
M. tuberculosis	Humans [1,19,28]	Cattle [108,109], non-human primates [110,111], dogs [112–114], cats [115], zoo animals e.g., black and white rhinos [116], African elephants, and Asian elephants [117–119], goats [120]
Mycobacterium africanum	Humans [121–123]	Cattle [124], rock hyraxes (*Procavia capensis*) [29,125]
Mycobacterium pinnipedii	Seals (*pinnipedts*) [126]	Humans [127,128], cattle [129]
Mycobacterium caprae	Goats, sheep, and pigs [130,131]	Humans [132]
Mycobacterium microti	Cats, pigs [133], bank vole, wood mouse, shrew [134]	Humans [135]
Mycobacterium orygis	Antelope, deer, waterbuck [136], oryxes, gazelles [137],	Humans [138]
Mycobacterium canettii	Humans [29,139–141]	-
Mycobacterium mungi	Banded mongooses [142]	-
Mycobacterium suricattae	Meerkats (*Suricata suricatta*) [143]	-
Chimpanzee bacillus	Chimpanzee (*Pan troglodytes*) [16]	-
Dassie bacillus	Rock hyraxes [14,144], meerkats [143,145]	-

2. The Epidemiology of TB at the Domestic–Wildlife–Human Interfaces

Targeted epidemiologic studies at domestic–wildlife–human interfaces provide a foundation for effective control, ecological management, surveillance, and eradication of TB [95,146–148]. Over the years, the advances in strain-typing methods (such as spoligotyping [149–151], variable number of tandem repeats [152–154], whole genome sequencing [143,155–159], and other tools for characterising MTBC pathogens [12,22,46,160–162] have improved the understanding of genotype distributions [154], demographic risk factors for disease [41,163,164], MTBC geographical distributions of infected animal populations [165,166], and transmission patterns [34,80,167,168]. Transmission and TB manifestations in some hosts are associated with age and sex risk factors [169]. For example, in white-tailed deer, the odds of being TB positive is greater in males than females [95,147,169], highlighting sex-based differences (possibly hormonal) that may influence the risk of TB.

Whole genome sequencing data of MTBC isolates have shown 7 lineage classifications that have different TB epidemiological consequences worldwide [170,171]. Human-adapted MTBC lineages such as *M. africanum* and *M. tuberculosis sensu stricto* are associated with specific geographical locations, variations in virulence, and transmission capacity [172–174]. In New Zealand, 782 *M. bovis* genomes (across 8261 locations) over 30 years were used to track TB outbreaks in domestic and wildlife herds [159], demonstrating the significance of whole genome sequencing in understanding infection and transmission patterns. Heterogenous transmission rates and infectivity of *M. bovis* are influenced by community and populations with animal movements playing a key role in TB epidemiology [175,176]. Modifications in animal husbandry practices and changes in ecological and population densities are some factors that can influence transmission events among animals as well as increase zoonotic risks to human populations [177]. For example, it has been shown that modern farming, environmental changes from deforestation, settlement, and expansion of agriculture intensifies TB transmission from animals to humans [177].

The epidemiology of TB in domestic animals such as cattle is well documented in the United States [169], the United Kingdom [178–180], Iran [181], Italy [154], France [175], and Spain [182]. However, similar studies in wildlife are limited to some reports from wildlife species such as buffaloes [70], lions [46,88,183], and rhinoceros [93,95,184]. Furthermore, in wildlife settings, the epidemiology and pathogenesis of TB in European badgers have been studied extensively in countries like the United Kingdom and Ireland [46,175]. Badgers are considered maintenance hosts due to their longevity and social structures and are implicated in TB transmission to cattle [147]. Studies have shown that *M. bovis* shed by badgers into the environment can result in transmission to other badgers and cattle (based on genetically related strains) [185,186]. Thus, it is important to fill gaps in epidemiological knowledge on the wide TB host range to improve the detection of infections and mitigate transmission in captive and free-ranging animals.

It has also been demonstrated that domestic animals and wildlife can be an important source of zoonotic pathogens for human populations, particularly in low-income countries [43,187–190]. Infection with *M. bovis* can result in zoonotic transmission affecting a wide variety of mammals [115,177,191,192]. The zoonotic risk factors include herding infected animals, working in meat abattoirs [108,193], consumption of unpasteurised milk [18,194–196], blood [18], and undercooked or raw meat [18,191,193,197]. The zoonotic transmission of tuberculosis from animals to humans and vice versa is an under-reported problem, with few reports on its magnitude, particularly in developing countries [188,198]. However, in recent years, veterinarians, researchers, the World Health Organisation, and the World Organisation for Animal Health have emphasised improving the knowledge base on TB zoonosis using multidisciplinary One Health approaches [41,196,199–203]. This approach should increase understanding of the effects of TB zoonosis on a global scale.

3. Response of Different Hosts to MTBC Infection?

3.1. Human TB Infection Stages

Characterising different stages of TB infection in humans is an active area of research [204,205], and is typically better understood compared to disease progression in animals [8,120]. A spectrum of clinical stages, ranging from infection clearance, LTB, incipient TB, subclinical TB, and active TB (ATB) disease, has been proposed (Table 2) [32,204]. However, approaches to diagnose, differentiate, and treat these stages are complicated, controversial, and inadequate [20].

Upon infection with pathogenic mycobacteria, there are several potential outcomes. Host defenses may clear the infection; alternatively, the infection may be contained in the form of LTB [146,206], or progress to ATB [204,207]. LTB is defined as an asymptomatic clinical state where individuals are not infectious but may have a risk of progression to active TB disease over time [58]. Characterising the LTB stage in humans is important to prevent disease progression, but it can be difficult to completely eradicate it with existing chemotherapeutic regimens [208]. Therefore, LTB continues to present a global health burden and a major risk factor for the development of ATB disease, particularly in immunocompromised individuals [20,209–211].

People with incipient and subclinical TB lack signs and symptoms of disease, while individuals with ATB disease exhibit coughing, night sweats, loss of appetite, weight loss, or yellowish purulent sputum. Symptomatic individuals are a risk to others since they can transmit infectious bacilli in aerosols through speaking, coughing, or sneezing [146,206]. The complex adaptative mechanisms of *M. tuberculosis* in the host [212], host genetic variation influencing TB susceptibility [28,213,214], host-pathogen interactions [171,215–218], pathogen-pathogen co-infections [105,219], and pathogen-non-tuberculous mycobacterial co-infections [220,221] further complicate the investigation of infection stages. The factors that determine the stages of infection in humans are still unclear but are believed to involve host immune responses and pathogen adaptation mechanisms [222,223].

The hypothesis that different TB infection stages in humans are associated with different mycobacterial metabolic states has been proposed [204,205]. For instance, LTB has been linked to subpopulations of bacilli that are (i) viable but non or slowly replicating (VBNR) [224,225], (ii) viable but non-culturable (VBNC) [226,227], and (iii) metabolically inactive dormant bacilli [228]. Broadly, these subpopulations are categorised in the reversibly drug-tolerant, but not genetically drug-resistant population, termed "persisters" [227,229–231]; as shown in (Figure 1). Persister bacteria appear to be associated with LTB, incipient and subclinical infection [204,232,233], while actively replicating (AR) mycobacterial populations are present in ATB [204]. Even though human TB research has progressed, additional research is needed to fully understand these hypothesised TB stages in humans.

Table 2. Hypothetical stages of mycobacterial infection and host–pathogen interactions in domestic and wild animals. Infection stages may vary in different species depending on the host's immune response and risk factors, as well as strain and infecting dose of *Mycobacterium bovis*. (Adapted and adjusted from [25,204]).

bTB Stage		Clinical Signs	Host–Pathogen Interactions
Uninfected		Absent	- No immune response, and no viable bacteria
Infected	Cleared infection	Absent	- Innate and/or adaptive immune system clears the bacteria - There may be no memory response, or the immune memory response may last for some time after the pathogen has been eliminated - No viable bacteria present
	Latent infection	Absent	- Detectable immune responses present - Viable and slow or non-replicating bacteria possibly present
	Subclinical infection	Absent	- A transition state from latency or initial/early infection to active disease - Viable and slow or non-replicating bacteria likely present along with a small proportion of actively replicating populations - Microbiological evidence of culturable bacteria - Radiographic, gross, or histopathological evidence of infection
	Active TB disease	Present	- Viable and replicating bacteria present - Clinical signs (e.g., coughing, weight loss, and lymphadenopathy) - The individual may be infectious (intermittent shedding) - It is relatively easy to find culturable bacteria depending on the location of infection and the type of samples used for analysis

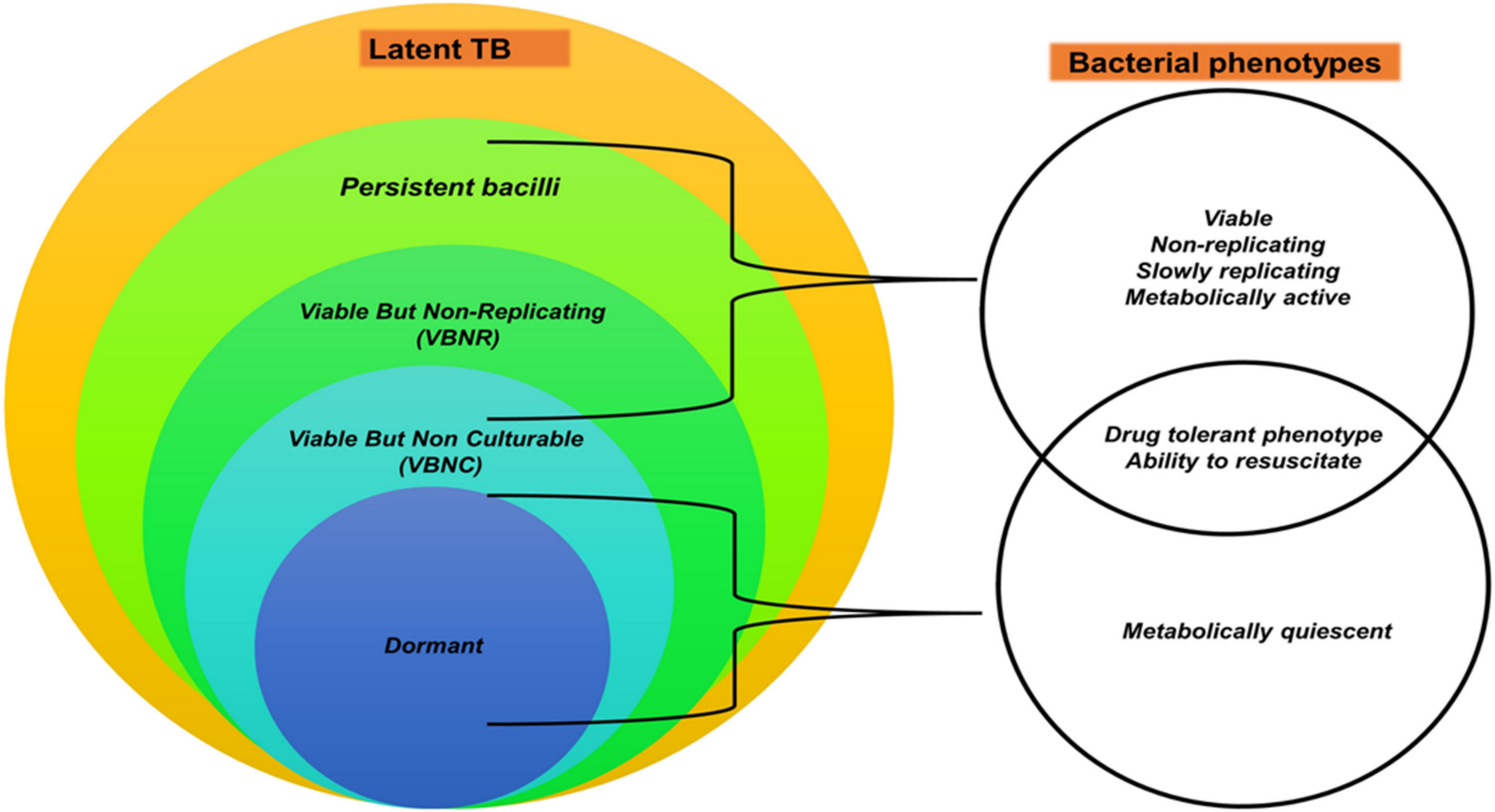

Figure 1. Latent TB stage and underlying bacterial phenotypes. Latent TB is speculated to encompass several bacterial phenotypes, under the broad heading of persister bacteria. The subpopulations of persister bacilli include viable but non-replicating (VBNR) bacilli, viable but non-culturable VBNC bacilli, and dormant bacilli. These have varying phenotypic characteristics and may vary with each TB stage. (Original figure).

3.2. Domestic and Wildlife Infection Stages of TB

Domestic animals are considered good models to understand TB pathogenesis and stages due to similar physiology, immunology, and anatomy to humans [30,234,235], and thus may be considered to further understand infection stages in other mammals. Transmission may occur after exposure to infectious secretions including saliva, aerosolised respiratory droplets, urine, faeces, exudate from fistulated lymph nodes, and ingestion of infected tissue by scavengers and predators [49,70,190]. The source of infection may influence the development of clinical signs, which can take months to years to appear, and include nonspecific changes, such as weight loss, reproductive failure, decreased milk production, lymphadenopathy, and coughing [6,8]. However, routes of MTBC infection vary in different host species and this may impact TB pathogenesis and influence the development of clinical signs depending on the number of bacterial loads of the source of infection [236]. Thus, the higher the bacterial load from the source of infection (i.e., ingestion of infected tissue from a TB diseased animal) the higher the likelihood of the infected individual developing clinical signs earlier than a source with a lower bacterial load (i.e., infected grass or water or soil) [18,237,238]. Additionally, signs and sites of infection can vary significantly in different species; for example, elbow hygromas and osteomyelitis in lions [46].

The wide range of animal hosts likely has different immune mechanisms, which would result in variable responses to MTBC infection [31,176,239], adding complications to our understanding of different TB stages. For example, elephants [118,240] and suids [241,242] have an early robust humoral response, whereas carnivores such as lions only develop humoral responses in the presence of disease [88,221,243]. Therefore, when conducting research these immune differences must be considered to improve understanding.

Extrapolation of techniques to diagnose human LTB to the study of natural MTBC infections in different species can be difficult due to the logistics of handling large or dangerous animals, long intervals between infection and development of clinical signs of disease, limited ability to identify the source and route of transmission, as well as a paucity of diagnostic tools [6,8,46,49]. The possibility of latent infections in cattle has been discussed in the literature, however, the evidence is not compelling [24,27,244]. Stages of MTBC infections have been hypothesised based on experimental [21,245] and veterinary field experiences with livestock and wildlife (Table 2). These include cleared infection, LTB, subclinical infection, and ATB disease, based on the presence of viable bacteria, detectable immune responses, clinical signs, and radiographic or gross pathological changes [222]. However, additional concrete evidence for these TB stages in animals is needed, which requires finding solutions to the aforementioned challenges and bridging knowledge gaps through research.

3.3. Diagnostic Challenges in Differential Stages of TB

Accurate diagnostic tests are crucial for controlling the spread of TB in humans and domestic, and wild animals [246]. Since animals can be infected with *M. bovis* (or some other MTBC members), definitive diagnosis relies on identifying the specific MTBC organism [247]. One key problem with the microbiological detection of mycobacteria antemortem is the assumption that the individual is shedding at the time of testing [204]. However, this approach is suboptimal, especially when using the limited antemortem samples available in animals, and often leads to false-negative results [74]. Even if MTBC infection is detected, there is a paucity of clinical and diagnostic tools to differentiate between putative LTB, incipient infection or subclinical infection, and ATB disease (Table 3) [248]. In addition, few studies have investigated differences in virulence and other characteristics of MTBC strains that may influence infection stages in animals [249,250].

Latent TB in humans is diagnosed by detectable antigen-specific immunological responses in the absence of clinical symptoms and evidence of pathological changes (Table 3) [4]. The QuantiFERON TB Gold In-tube Plus interferon-gamma release assay is used in human patients that are asymptomatic, lack radiographic changes, and are sputum

smear, culture, or PCR negative, to identify LTB [204,206,222]. However, validated mycobacterial antigen-specific IGRAs are only available for a handful of animal species [12], and radiography is limited by the size of the animal as well as logistics, especially with wildlife [28]. For example, presumptive *M. tuberculosis* infection in Asian elephants has been diagnosed using serological responses to specific mycobacterial antigens [240]. However, these individuals may be asymptomatic for years before confirming infection by the culture of trunk wash, tracheobronchial lavage fluids, or post-mortem tissue, and the presence of pathological changes [46].

Since existing TB diagnostic tools can not differentiate between stages of TB infection, any positive test for bovine TB (bTB) usually results in the culling of positive animals, regardless of whether clinical signs or lesions are present [35]. In these cases, a post-mortem inspection may aid in determining if possible latent, subclinical, and active infection is present [241,251]. For example, there are reports of cattle with positive immunological assay results but with no evidence of disease, which could be consistent with LTB [26]. These animals lacked gross and histopathological lesions, yet in vivo TST or in vitro blood-based mycobacterial antigen-specific IGRA was positive, although mycobacterial culture results were negative (Table 3) [26,241,252,253]. Often these animals were considered to have false-positive immunological test results rather than the possibility of having LTB. However, other explanations include suboptimal culture detection in paucibacillary samples or false-positive immunologic test results [26].

In summary, many of the tools available to diagnose LTB in humans are unavailable or have not been thoroughly investigated in animals. There is a lack of validated TB diagnostic tests, which often require species-specific approaches [241]. In animals, respiratory samples are rarely submitted for mycobacterial culture and PCR, due to a paucity of veterinary diagnostic laboratories capable of performing these techniques. Therefore, unless there is a suspicion of TB, the lack of diagnostic workup in animals, especially in wildlife, results in a large knowledge gap to demonstrate the possibility of LTB and other possible infection stages.

Table 3. Hypothetical infection stages and associated antemortem and postmortem test results for categorising TB stages.

Animal TB Stage (a)		**Antemortem Tests (b,c)**		**Postmortem Tests (d)**	
		TST	**IGRA**	**Bacterial Culture**	**Tissue Histopathology Consistent with bTB (Yes/No)**
Uninfected		Negative	Negative	Negative	No
Infected	Cleared infection	Negative (innate immune system clearance) Positive (adaptive system immune clearance)	Positive for a short period before waning (adaptive immune clearance)	Negative	No
	Latent infection	Positive	Positive	Negative	No
	Subclinical infection	Positive	Positive	Positive	Yes (early-stage granulomas)
	Active disease	Positive	Positive	Positive	Yes (multifocal and/or confluent late-stage granulomas

TST = tuberculin skin test, IGRA = interferon-γ release assay. References: **a** [204], **b** [26,254,255], **c** [256,257], **d** [24,25,131,222].

4. The Influence of MTBC Characteristics on TB Stages

Eleven MTBC ecotypes evolved from *M. canettii* including *M. tuberculosis* and *M. bovis* which are 99.95% genetically similar, and the primary causative agents of TB in humans and animals, respectively [29,249]. MTBC genotyping in different hosts has been studied across Africa including countries like South Africa, Mozambique, Algeria, and Ethiopia with *M. bovis* being the key aetiological pathogen for animal TB [258].

Despite primarily infecting humans, *M. tuberculosis* can occasionally infect domestic animals and wildlife [118,259]. Furthermore, *Mycobacterium bovis* and *M. tuberculosis* share some similar patterns of transmission and pathogenesis [21,25], however, there are genetic [260–262], metabolic [263,264], and physiological differences [249,250] between *M. bovis* and *M. tuberculosis* [265], and among *M. bovis* [266] and *M. tuberculosis* [267] strains. These differences could affect granuloma formation [23,268], replicative states during infection, and subsequent infection stages in humans and animals.

M. tuberculosis phenotypic heterogeneity has been observed during different in vitro stress conditions such as macrophage exposure and acid stress [214,225,269]. Mouton et al. [225] demonstrated that during macrophage infection, intracellular *M. tuberculosis* showed a relatively homogeneous population structure at early time points, with a similar replication rate at 24 h to the in vitro-cultured bacteria. Yet, from 48 h onwards, a more diverse population emerged, with a distinct slower-growing population at 96 h, demonstrating the ability of *M. tuberculosis* to adapt to stress. However, there are relatively few studies on *M. bovis* phenotypic heterogeneity under in vitro stressors [268]. Therefore, application of in vitro and in vivo stress models, previously utilised for *M. tuberculosis*, to *M. bovis* could reveal new insights into replication dynamics and adaptation to stress.

Similar to *M. tuberculosis* [264,265,269–271], in vitro and in vivo studies using *M. bovis* BCG have investigated replication dynamics under different host stressors [117,121–124]. Results demonstrated how human alveolar macrophages effectively used nitric oxide production as a mechanism to suppress *M. bovis* BCG growth [272], similar to observations with *M. tuberculosis* [273]. In addition, 23 genes likely involved in energy metabolism were downregulated while only a *nar*X gene (encoding nitrate reductase) was upregulated in aerobic dormant BCG [274], suggesting this gene plays a role in dormancy responses, similar to *M. tuberculosis*. Boon and Dick [275] revealed that the dormancy survival regulator (*dos*R) dormancy survival regulator gene that encodes for Rv3133c (α-crystallin small heat shock protein), universal stress protein encoded by Rv2623, and cystathionine β-synthase protein encoded by Rv2626c were upregulated in *M. bovis* BCG during anaerobic conditions. These findings were similar to the behaviour shown by *M. tuberculosis*, in which these genes induced non-replicating or dormant bacilli. Furthermore, the differential abilities of MTBC species to enter a non-replicative state was demonstrated using a rabbit model whereby extrapulmonary tuberculosis was exclusively observed in *M. bovis* Ravenel and *M. bovis* AF2122/97 compared to *M. tuberculosis* CDC1551 and *M. tuberculosis* H37Rv [267].

Adaptation to stressors may provide a greater understanding of differences in the ability of MTBC to become dormant. Exposure of *M. bovis* CRBIP7.106 (isolated from human bone) to cryogenic treatment and nutrient starvation resulted in stress responses including morphological phenotypic adaptation through the formation of rare extreme morphologic forms (L-forms or cell-wall deficient) bacteria [276], likely to be a long-term survival strategy during unfavourable conditions. Similar to *M. tuberculosis*, Rv3134c/devR/devS in *M. bovis* BCG Pasteur strain 1137P2 was responsible for adaptation during nutrient starvation, ex vivo macrophages, and oxygen limitation [277], which would be necessary to create an LTB state. Using a nutrient starvation model, the presence and expression of key genes such as (*mpb83*, *mpb70*, *mmpL8-papA1-pks2* locus, *Mb2651*) that synthesise or encode cell wall, lipid metabolism, and transcriptional regulators, respectively, differed between *M. tuberculosis* H37Rv and *M. bovis* AF2122/97 [260]. For example, a lipid metabolism *mmpL8-papA1-pks2* locus was present only in *M. tuberculosis*. *Mpb83* (encoding cell wall lipoprotein), and *mpb70* (encoding immunogenic lipoprotein) genes were upregulated in *M. bovis* compared to *M. tuberculosis*. In addition, transcriptional regulators showed different patterns with increased

expression of *Mb2651*, *Mb2654c*, *Mb3109c/virS*, *Mb3477c* in *M. bovis*, and *Rv0196*, *Rv0275c*, and *Rv2160A-Rv2160c* in *M. tuberculosis*. These observations emphasise the differential way in which the MTBC strains may respond or adapt to stress, thus impacting the ability to result in LTB. Therefore, research into bacterial characteristics that influence host-pathogen interactions and bacterial virulence is essential to elucidate their role in LTB.

Reactivations of *M. tuberculosis* infection in humans are well documented [226,278,279]. Similarly, there are reports of *M. bovis* infection reactivations in elderly people in England [280], immunocompromised elderly from Demark [281] and the Netherlands [163], and in bTB eliminated areas (1% of total cases) [282], suggesting a possible capacity of *M. bovis* to persist in a latent state in humans. In addition, LTB was diagnosed in Mexican abattoir and dairy farm workers infected with *M. bovis;* 76.2% were TST positive and 58.5% IGRA positive [4]. Additionally, cases of BCG infection (BCG-osis) have been reported weeks to months after BCG vaccination in children, suggesting that *M. bovis* BCG can enter a non-replicative persister state as well as reactivate [283,284]. However, more studies are needed to establish *M. bovis* persistence and investigate the relationship between metabolic states of mycobacteria and different infection stages in animals.

5. Candidate Models to Improve Understanding of TB Stages in Animals

5.1. In Vitro Models

Numerous in vitro experiments have been performed to understand LTB in humans, with a relative paucity of corresponding work using *M. bovis*. In vitro models are pivotal for simulating the microenvironment that mycobacterial pathogens may encounter in human and animal hosts [285,286]. To date, nine variations of hypoxia models have been exploited for *M. tuberculosis* studies [287], while very few have been applied to *M. bovis* strains, although attenuated *M. bovis* BCG strains have been investigated under hypoxic conditions [274]. In one report, *M. bovis* BCG was found to survive and adapt to hypoxia through upregulation of DosR (Rv3133c), an essential dormancy response regulator also found in *M. tuberculosis* [275]. Gideon et al. [288] demonstrated upregulation of genes from the regions of difference (RD) 2 (Rv2659c) and RD11 (Rv2658c) in *M. tuberculosis* during hypoxia [261]. However, RD11 is absent in all *M. bovis* strains, so the hypoxic adaptive advantage this RD region may confer on *M. tuberculosis* would be lost in *M. bovis*. Furthermore, RD2 is absent in *M. bovis* BCG, so this strain may not fully represent the adaptation of *M. bovis* virulent strains [261]. Therefore, it is important to shift research focus from *M. bovis* BCG and commonly applied lab-adapted virulent *M. bovis* Ravenel and *M. bovis* AF2122/97 to pathogenic *M. bovis* strains isolated from animals with natural infections [266]. This approach will build new knowledge on how pathogenic wild-type strains would respond to hypoxia.

Nutrient starvation, acid stress, and multi-stress models that combine single stressors [hypoxia (5% O_2 content), high CO_2 (10%), nutrient deprivation (10% Dubos medium), and acidic pH (pH 5.0)] [289] have been explored using *M. tuberculosis* to mimic multiple host-pathogen interactions upon infection [289]. However, the use of these models with *M. bovis* has been limited. In vitro nutrient starvation of *M. bovis* BCG induced upregulation of the *Rv3134c/devR/devS* transcriptional regulator, which is also present in *M. tuberculosis* [277]. Further, *M. bovis* BCG was found to be tolerant of low pH through the adoption of a homeostatic balance between the internal and external pH [290]. Another study found that *M. bovis* BCG was also tolerant to low pH in the presence of glutamate as a carbon source [291]. These results highlight that in an acidic environment, a subpopulation of *M. bovis* bacilli, which can utilise glutamate as a carbon source, may have the ability to persist longer than those that cannot utilise glutamate. Thus, these in vitro models appear to be a potential platform for additional investigations using field strains of *M. bovis*.

In vitro macrophage infection models have been widely applied to understand differences in pathogenesis and host tropism in *M. bovis*, *M. tuberculosis* [265], *Mycobacterium avium subsp. paratuberculosis*, and *Mycobacterium avium subsp. avium* [292]. Bovine alveolar macrophages [265], blood-derived macrophages [293], human monocyte THP-1 [294],

and RAW 264.7 macrophages [295,296] have been used to understand mechanisms that *M. bovis* employs to adapt to stress, host-pathogen interactions, and vaccine discovery. Bovine alveolar macrophages infected with *M. bovis* BCG and two virulent *M. bovis* strains (*M. bovis* Ravenel and *M. bovis* AF2122/97) have revealed transcriptional and proteomic differences between *M. bovis* and *M. tuberculosis* pathogens under acid shock, hypoxia, and macrophage infection [260,297–299]. These studies showed that *M. tuberculosis* expressed higher levels of nitrate reductase-associated genes *narG* and *narH*, while *M. bovis* expressed more *mpb70* and *mpb83* (the two most upregulated genes of the overall analysis) [260,298]. A cell wall-associated protein, DipZ (member of sigK regulon), that encodes for MPB70 and MPB83, was among the top ten highly expressed proteins in *M. bovis* compared to *M. tuberculosis* under stress conditions. Additionally, Rv0188, an enduring hypoxic response antigen, was found to be solely associated with low pathology scores in cattle infected with *M. bovis*, suggesting that it may play a role in inducing a non-replicative state [300]. These genes and protein expression differences could potentially influence TB stages in humans and animals [27]; however, additional studies are needed to investigate their effects on the development of LTB using diverse hosts [28,301,302] and MTBC strains. Since bovine alveolar macrophages are isolated from cattle, this model may be considered a more physiologically relevant model for *M. bovis* and thus suitable for understanding the host-pathogen interactions during *M. bovis* infections.

5.2. In Vivo Models

Cattle are the most commonly used animals for investigating in vivo *M. bovis* pathogenesis and host-pathogen interactions [25,300,303]. Although cattle are a natural host of *M. bovis*, they may not recapitulate infection stages in the wide variety of other animal species infected with *M. bovis* [268,304]. Experiments to study LTB using cattle have a logistical challenge since there are limited antemortem methods to confirm whether pathological changes are present or absent [244]. Cattle experimentally infected with *M. bovis* often develop clinical signs and progress to disease [268], whereas infections with *M. tuberculosis* H37Rv or other *M. tuberculosis* isolates are reported to delay progression to disease [31,120,244]. Therefore, *M. bovis* dose-response and strain differences in experimental infection models need further exploration.

Domestic pigs have been recently used as a model to understand domestic animals and human TB [30,305–307]. Pigs experimentally infected with *M. bovis* AF2122/97 exhibited greater morbidity, rapid onset mortality, severe pathology, and weight loss, as compared to less severe disease in those infected with *M. tuberculosis* Erdman [30]. *M. tuberculosis*-challenged pigs developed the active disease but had delayed onset of fever, no signs of respiratory distress, and showed no change in health status, compared to *M. bovis* infection, during the 35-week trial [30]. Therefore, the pig model may be useful for exploring whether different *M. bovis* field strains develop different infection stages compared to the commonly used *M. bovis* AF2122/97 and *M. bovis* Ravenel strains.

The badger is a promising in vivo model for studying LTB in animals [21,308,309]. This model mimics observations in naturally *M. bovis*-infected animals, with up to 80% of infected badgers containing *M. bovis* for years, until reactivation occurs when their immune system becomes compromised [308,309]. Chronic progressive pulmonary TB occurs in badgers, therefore this model may be a candidate system for not only LTB but also for subclinical infection studies [308].

The Cornell mouse model is considered a "classic" TB latency model, in which infected mice are treated with antibiotics to reduce bacteria to undetectable levels, before TB reactivation [279,310]. This model results in a steady asymptomatic state that resembles human latency in which bacteria enter a slowly or non-replicating state [205,311–313]. A study found that mice vaccinated before being challenged developed different immunopathology, with *M. bovis* BCG challenged mice having lower histopathological scores than those challenged with *M. tuberculosis* [314]. Although this is not surprising since BCG is attenuated, it

raises the question of whether virulent *M. bovis* strains would differ in their ability to enter a slowly or non-replicating state in this model.

The guinea pig TB model has also been used to study infection stages [315], *M. bovis* diagnostics [316], and vaccine development [317]. This has been used to study LTB using *M. tuberculosis* [318] but hasn't been evaluated using *M. bovis* clinical strains. Mice and guinea pig models are relatively cheaper than those using large animals, such as cattle and pigs, although they can be technically challenging and present limitations such as lack of granuloma structure and organisation, no extracellular dissemination, and difficulty establishing LTB without vaccinations [222,317,319] Therefore, badgers, cattle, and pigs may be more physiologically relevant to studying the different TB stages in *M. bovis* natural hosts.

In vivo research is needed to answer questions about the existence of different TB stages in animals. Although cattle, pig, and badger models appear to be the most appropriate models, they do not produce all features of the different TB stages or reflect the diverse host-pathogen repertoire of responses during infection in other domestic animal and wildlife species [314,315,320].

6. Candidate Host and Pathogen Biomarkers to Improve Understanding of TB Stages

6.1. Candidate Host Markers

Currently, there are no specific host immunologic biomarkers definitively associated with latency in humans and animals because most overlap with those for active disease [48,223,285,321], although in vitro and in vivo models have shed light on possible candidates [205]. A quantitative comparison of cytokine levels in the blood of latently infected versus actively diseased patients showed differences in tumor necrosis factor α, IFN-γ, and interleukin 12 (IL-12) [26,48,205]. Transcriptomic profiling of immune responses in a Gambian study found that an antiapoptotic gene *bcl2* was a promising marker that indicated the onset of active disease very early after infection [322]. In addition, the study found that the B-cell lymphoma 2 (BCL2) marker was significantly lower in individuals with ATB disease versus latently infected individuals [322], also making it a potential host candidate biomarker. Another study found that IL-13 and autoimmune regulator (AIRE) were biomarkers that could identify high-risk people with LTB that develop ATB, months before clinical diagnosis [323].

Multiple cytokine assays have been evaluated in human studies for their ability to differentiate active disease from LTB [324,325]. Suzukawa et al. [326] found that combined analysis of IFN-γ, IL-2, IL-5, IL-10, IL-1RA, and MCP-1/CCL2 cytokines found in QuantiFERON supernatant, could distinguish ATB from LTB in humans. In a recent study, in vitro antigen-specific concentrations of IFN-γ, IL-2, IL-5, IL-10, IL-1RA, and monocyte chemoattractant protein-1 (MCP-1/CCL2) showed promise for distinguishing ATB from LTB [321,326]. A recent systematic review that compared human host factors involved in LTB, identified IL-1, IL-6, IL-9, IL-17, and IL-IRA as potential candidates for identifying human latency [48].

In contrast, there are relatively few studies on diagnostic host biomarkers in animal TB, with the majority focusing on developing diagnostic tools and investigating pathogenesis [12,21,31,252]. Therefore, additional investigation is needed to confirm whether these can be used to detect latent infection in animals. The development of an LTB cytokine panel would need to consider the variability of MTBC characteristics, including bacterial heterogeneity, host immunological responses, and pathogenesis, across animal species.

6.2. Candidate Pathogen Biomarkers

Several mycobacterial factors are upregulated during *M. tuberculosis* infection in response to host defences. In human LTB, these include genes that mediate energy metabolism, lipid production, stress response, growth restriction, hypoxia response, and toxin-antitoxin stress gene regulators of the bacilli [205,227,327]. By extrapolating from

human LTB to animals, candidate bacterial biomarkers to investigate would be DosR and other transcriptional factors.

The DosR regulon is one of the best-studied regulatory systems in mycobacterial responses to anaerobic conditions [275,328]. DosR is responsible for the maintenance and upkeep of mycobacterial persister populations believed to underlie latency and is conserved in *M. tuberculosis* [227,329–331] and *M. bovis* [277]. This regulon is a 48-component system controlled by the DosR regulator [270]. *Dos*R genes include *nrdZ*, *narX*, *narK2*, *ctpF*, *otsB1*, *fdxA*, *pdxA*, *pfkB*, *acr*, *acg*, and *dosR*, which respond to environmental stress conditions, leading to mycobacterial dormancy and persistence [270,332–334]. The DosR antigen Rv2031c (Acr or HspX) has been associated with adaptation to stressful in vitro conditions such as hypoxia [297,335]. Importantly, studies in cattle infected with *M. tuberculosis* H37Rv and *M. bovis* AF2122/97 [244] have demonstrated that this antigen may differentiate between active disease and possible LTB in animals.

A recent study has recognised the potential of DosR and resuscitation-promoting factors (Rpf) antigens [Rv2029c (PfkB), Rv2389c (RpfA), Rv0867c (RpfA), and E6-C1] to discriminate between LTB and ATB in a TB endemic human population [330]. Similar results have been observed in other studies conducted in African, Asian, European, Indian, and Brazilian populations [330,331,336], suggesting that DosR antigens are important for latency, independent of host immune responses, environmental background, human genetics, and circulating *M. tuberculosis* strains. Furthermore, a study by Jones et al. [300] identifies potential LTB markers in naturally infected cattle such as DosR/S/T antigens (Rv2627c, Rv2628, Rv2029c, and Rv1733c). However, the number of animals with no visible lesions was very low, so LTB may have been missed due to the experimental conditions. Therefore, studies with a larger sample size would provide further clarity and a better understanding of LTB biomarkers.

The main driver for latent *M. tuberculosis* infection is believed to be hypoxia [288], but more recent studies have discovered additional factors that could play a role. Transcription of mRNA sigma factor genes is implicated in different stress responses and may play a role in the adaptation to stressful host environments [337]. These include sigma factor F gene (*sigF*) (responsible for slowing growth of bacteria) [338,339], and *hspX*/ *acr*/ *Rv2031c* genes that encode for the α-crystallin homolog, and small heat shock protein (sHSP16.3) [340,341]. *SigF* is upregulated in *M. tuberculosis* persisters, suggesting a role in latency [332]. Further, the *sigF* gene is responsible for regulating oxidative stress, antibiotic stress, cold shock, and nutrient depletion [332,337]. Sigma factor B (*sigB*) and *sigH* are additional genes induced by heat and oxidative stress [342,343]. Although *sigF* has been demonstrated to be induced in hypoxic conditions and the stationary growth phase in *M. bovis* BCG [337,344], there is a need to further investigate transcriptional factors specifically involved in *M. bovis* persister bacilli.

The tools and methods to study *M. tuberculosis* persistence have improved in recent years, hence some mycobacterial candidate genes for persistence may overlap in *M. tuberculosis* and *M. bovis* strains due to their genetic similarities. These similar genetic characteristics could make it easier to reproduce models using *M. bovis* or other MTBC species, thus accelerating latency research in animals. Nevertheless, some of the physiological differences between these strains may reveal unique candidate genes for latency upon infection and this must be taken into consideration during experimental design.

7. How Can Researchers Bridge Existing LTB Knowledge Gaps in Animals?

Although laboratory-based research has highlighted the divergent nature of *M. tuberculosis* and *M. bovis* infection stages in mice [314], guinea pigs [290], cattle [31], badgers [21], and domestic pigs [307,345], there is still no compelling evidence on whether LTB occurs in domestic and wild animals infected with *M. bovis*, *M. tuberculosis*, or other MTBC pathogens. Therefore, there is a need to identify knowledge gaps and possible approaches to address these.

7.1. Factors Contributing to Existing Knowledge Gaps

- A paucity of studies describing and comparing the pathogenesis of *M. bovis* infection and other MTBC species in different animal species.
- Limited availability of sensitive and specific diagnostic tools for detection and differentiation of MTBC infection stages in domestic animals and wildlife, especially antemortem tests.
- Incomplete information on the diversity of MTBC virulent clinical strains, primarily *M. bovis*, and their influence on pathogenesis.
- A limited understanding of the role and variability in immune responses to mycobacterial infection in different animal species.
- A poor understanding of the genetic, metabolic, and physiological characteristics of *M. bovis* could promote persister bacilli formation.
- A lack of clarity on how TB stages vary in different hosts (humans, domestic and wild animals).
- A lack of well-characterised in vitro and in vivo models of *M. bovis* infection to simulate different stages of infection, including LTB.

7.2. Recommendations for Future Research

To improve understanding of LTB in animals, data from in vitro and in vivo MTBC archetypal strains (such as *M. tuberculosis* H37Rv, *M. tuberculosis* CDC1551, *M. bovis* Ravenel, and *M. bovis* AF2122/97) and studies on host responses in *M. tuberculosis* and *M. bovis* BCG infections should be used to design future research. This should include:

- Developing a consensus on the definition of latency in domestic and wild animals and identifying a model that could be used to find biomarkers for this state.
- Identification of blood-based host and pathogen biomarkers that can differentiate between ATB and different stages of *M. bovis* infection in different animal species.
- Utilising available tools to study the phenotypic state of persister bacilli at a single-cell level to understand the physiological, phenotypic, and molecular features of different strains.
- Comparing the pathogenesis of *M. bovis* and other MTBC in different animal species to characterise the chronic asymptomatic state in infected hosts.
- Exploring host–pathogen similarities and differences of host–pathogen interactions to elucidate factors leading to LTB and susceptibility of different species to latent infections.

8. Conclusions

Animal TB research is still lagging compared to human TB research. Reasons include the complexity introduced by the fact that animals can be infected by a wide range of MTBC species, and a range of animal species can be infected by *M. bovis* [176]. Further, each MTBC species has diverse strains which could have differential influences on their pathogenesis and virulence. There is a lack of compelling evidence to prove the existence of different TB stages in animals as proposed in humans [204]. Experimental cattle [31] and pig studies [30], that applied laboratory-adapted strains, suggest that *M. bovis* is less likely to enter a persister state than *M. tuberculosis*. Comparative genetic and proteomic studies of *M. bovis* and *M. tuberculosis* have shown metabolic and replicative differences which could impact how these pathogens adapt to different animal hosts [249,250]. Despite these genetic and proteomic differences, reports of *M. bovis* reactivation in humans suggest that this species is capable of establishing LTB. However, further investigations are needed to ascertain the likelihood of MTBC pathogens (especially *M. bovis*) establishing LTB in animals and humans [250,267].

Although there is a lack of compelling evidence for latency in cattle [27,160], some antemortem and post-mortem findings suggest a possible LTB stage in animals [21,26,131,308]. Latent TB could occur in some animal species but is under-recognised due to the lack of defined criteria for TB stages, the challenging logistics, and the lack of diagnostic tools that can differentiate between several infection stages. However, there are promising ap-

proaches to studying human LTB that could serve as a foundation to elucidate this stage in animals [204]. Blood-based test approaches present a convenient way to distinguish TB stages ante-mortem; however, the current biomarkers of LTB and active disease overlap [326]. While post-mortem tests can also be applied to validate LTB in animals they can only be performed upon culling an individual, therefore presenting feasibility and cost implications. These myriad challenges negatively impact the progress of research to determine if LTB occurs in domestic or wild animals, however, using cross-species studies (*M. bovis* vs. *M. tuberculosis*) could advance understanding of LTB at the domestic-wildlife-human interfaces.

Identifying TB stages such as LTB in animals can inform policy, devise targeted management, and improve control strategies based on associated risks. Studying LTB in animals could also differentiate individuals that may be infected but not infectious from those with a greater risk of spreading the disease, provide potential management changes that could prevent infected animals from progressing to active disease (and therefore spread) and minimise the loss of animals due to unnecessary culling (especially for endangered animals such as rhinos). In vitro and in vivo models can be applied to broaden knowledge on whether different field MTBC species, particularly *M. bovis*, induce persister bacilli believed to underlie LTB. When designing such studies, it is important to be aware of the diversity in host-pathogen interactions and infection outcomes in different animals. Moreover, the knowledge gained from animal TB research can also inform models to study LTB in humans. Future research should also focus on methods to further identify persister bacterial populations, not only in culture but also directly in animal samples to characterize their phenotypes, ultimately bridging some LTB knowledge gaps.

Author Contributions: All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication. P.N. performed conceptualisation, investigation, writing (original draft, review, and editing), and visualisation; B.B. performed conceptualisation, and writing (original draft, review, and editing), W.J.G. performed writing (original draft, review, and editing) and supervision; M.A.M. and S.L.S. performed conceptualisation, funding acquisition, supervision, and writing (original draft, review, and editing). The opinions expressed in this paper are solely those of the authors. All authors have read and agreed to the published version of the manuscript.

Funding: The authors acknowledge Stellenbosch University Faculty of Medicine and Health Science, the South African Medical Research Council (SAMRC), and the National Research Foundation (NRF) South African Research Chairs Initiative (SARChI grant numbers 86949 and 86539) for financial support. The content is the sole responsibility of the authors and does not necessarily represent the official views of the South African Medical Research Council or the National Research Foundation.

Acknowledgments: We also acknowledge constructive discussions and contributions from Jomien Mouton, and Trisha Parbhoo.

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The authors declare that there are no conflict of interest.

References

1. WHO. Global Tuberculosis Report. 2021. Available online: https://www.who.int/publications/i/item/9789240037021 (accessed on 9 May 2022).
2. Tadesse, T.; Lelo, U.; Markos, T.; Tadesse, T.; Birhan, F.; Tona, T. Review on the Epidemiology, Public Health and Economic Importance of Bovine Tuberculosis. *J. Biol. Agric. Healthc.* **2017**, *7*, 16–23.
3. Lesslie, I.W.; Magnus, K.; Stewart, C.J. The Prevalence of Bovine Type Tuberculous Infection in Man in the English Rural Population. *Tubercle* **1972**, *53*, 198–204. [CrossRef]
4. Torres-Gonzalez, P.; Soberanis-Ramos, O.; Martinez-Gamboa, A.; Chavez-Mazari, B.; Barrios-Herrera, M.T.; Torres-Rojas, M.; Cruz-Hervert, L.P.; Garcia-Garcia, L.; Singh, M.; Gonzalez-Aguirre, A.; et al. Prevalence of Latent and Active Tuberculosis among Dairy Farm Workers Exposed to Cattle Infected by *Mycobacterium bovis*. *PLoS Negl. Trop. Dis.* **2013**, *7*, e2177. [CrossRef]

5. Kanabalan, R.D.; Lee, L.J.; Lee, T.Y.; Chong, P.P.; Hassan, L.; Ismail, R.; Chin, V.K. Human Tuberculosis and *Mycobacterium tuberculosis* Complex: A Review on Genetic Diversity, Pathogenesis and Omics Approaches in Host Biomarkers Discovery. *Microbiol. Res.* **2021**, *246*, 126674. [CrossRef]
6. Miller, M.A.; Lyashchenko, K.P. 15 Mycobacterial Infections in Other Zoo Animals. In *Tuberculosis, Leprosy and Mycobacterial Diseases of Man and Animals: The Many Hosts of Mycobacteria*; CABI: London, UK, 2015. [CrossRef]
7. Zanardi, G.; Boniotti, M.B.; Gaffuri, A.; Casto, B.; Zanoni, M.; Pacciarini, M.L. Tuberculosis Transmission by *Mycobacterium bovis* in a Mixed Cattle and Goat Herd. *Res. Vet. Sci.* **2013**, *95*, 430–433. [CrossRef]
8. Pesciaroli, M.; Alvarez, J.; Boniotti, M.B.; Cagiola, M.; Di Marco, V.; Marianelli, C.; Pacciarini, M.; Pasquali, P. Tuberculosis in Domestic Animal Species. *Res. Vet. Sci.* **2014**, *97*, S78–S85. [CrossRef] [PubMed]
9. Muñoz Mendoza, M.; de Juan, L.; Menéndez, S.; Ocampo, A.; Mourelo, J.; Sáez, J.L.; Domínguez, L.; Gortázar, C.; García Marín, J.F.; Balseiro, A. Tuberculosis Due to *Mycobacterium bovis* and *Mycobacterium caprae* in Sheep. *Vet. J.* **2012**, *191*, 267–269. [CrossRef]
10. Hang'ombe, M.B.; Munyeme, M.; Nakajima, C.; Fukushima, Y.; Suzuki, H.; Matandiko, W.; Ishii, A.; Mweene, A.S.; Suzuki, Y. *Mycobacterium bovis* Infection at the Interface between Domestic and Wild Animals in Zambia. *BMC Vet. Res.* **2012**, *8*, 221. [CrossRef]
11. Olivier, T.T.; Viljoen, I.M.; Hofmeyr, J.; Hausler, G.A.; Goosen, W.J.; Tordiffe, A.S.W.; Buss, P.; Loxton, A.G.; Warren, R.M.; Miller, M.A.; et al. Development of a Gene Expression Assay for the Diagnosis of *Mycobacterium bovis* Infection in African Lions (*Panthera leo*). *Transbound. Emerg. Dis.* **2017**, *64*, 774–781. [CrossRef]
12. Bernitz, N.; Kerr, T.J.; Goosen, W.J.; Chileshe, J.; Higgitt, R.L.; Roos, E.O.; Meiring, C.; Gumbo, R.; de Waal, C.; Clarke, C.; et al. Review of Diagnostic Tests for Detection of *Mycobacterium bovis* Infection in South African Wildlife. *Front. Vet. Sci.* **2021**, *8*, 588697. [CrossRef]
13. Malone, K.M.; Gordon, S.V. *Mycobacterium tuberculosis* Complex Members Adapted to Wild and Domestic Animals. *Adv. Exp. Med. Biol.* **2017**, *1019*, 135–154. [CrossRef] [PubMed]
14. Mostowy, S.; Cousins, D.; Behr, M.A. Genomic Interrogation of the Dassie Bacillus Reveals It as a Unique RD1 Mutant within the *Mycobacterium tuberculosis* Complex. *J. Bacteriol.* **2004**, *186*, 104–109. [CrossRef] [PubMed]
15. Brites, D.; Loiseau, C.; Menardo, F.; Borrell, S.; Boniotti, M.B.; Warren, R.; Dippenaar, A.; Parsons, S.D.C.; Beisel, C.; Behr, M.A.; et al. A New Phylogenetic Framework for the Animal-Adapted *Mycobacterium tuberculosis* Complex. *Front. Microbiol.* **2018**, *9*, 2820. [CrossRef] [PubMed]
16. Coscolla, M.; Lewin, A.; Metzger, S.; Maetz-Rennsing, K.; Calvignac-Spencer, S.; Nitsche, A.; Dabrowski, P.W.; Radonic, A.; Niemann, S.; Parkhill, J.; et al. Novel *Mycobacterium tuberculosis* Complex Isolate from a Wild Chimpanzee. *Emerg. Infect. Dis.* **2013**, *19*, 969. [CrossRef]
17. Gummow, B. A Survey of Zoonotic Diseases Contracted by South African Veterinarians. *J. S. Afr. Vet. Assoc.* **2003**, *74*, 72–76. [CrossRef]
18. Sichewo, P.R.; Vander Kelen, C.; Thys, S.; Michel, A.L. Risk Practices for Bovine Tuberculosis Transmission to Cattle and Livestock Farming Communities Living at Wildlife-Livestock-Human Interface in Northern Kwazulu Natal, South Africa. *PLoS Negl. Trop. Dis.* **2020**, *14*, 7681. [CrossRef]
19. Moyo, M.; Lebina, L.; Milovanovic, M.; MacPherson, P.; Michel, A.; Martinson, N. Tuberculosis Patients at the Human-Animal Interface: Potential Zooanthroponotic and Zoonotic Transmission. *One Health* **2021**, *13*, 100319. [CrossRef]
20. Behr, M.A.; Edelstein, P.H.; Ramakrishnan, L. Revisiting the Timetable of Tuberculosis. *BMJ* **2018**, *362*, k2738. [CrossRef]
21. Gormley, E.; Corner, L.A.L. Pathogenesis of *Mycobacterium bovis* Infection: The Badger Model as a Paradigm for Understanding Tuberculosis in Animals. *Front. Vet. Sci.* **2018**, *4*, 247. [CrossRef]
22. Michel, A.L.; Lane, E.P.; de Klerk-Lorist, L.M.; Hofmeyr, M.; van der Heijden, E.M.D.L.; Botha, L.; van Helden, P.; Miller, M.; Buss, P. Experimental *Mycobacterium bovis* Infection in Three White Rhinoceroses (*Ceratotherium simum*): Susceptibility, Clinical and Anatomical Pathology. *PLoS ONE* **2017**, *12*, e0179943. [CrossRef]
23. Palmer, M.V.; Kanipe, C.; Boggiatto, P.M. The Bovine Tuberculoid Granuloma. *Pathogens* **2022**, *11*, 61. [CrossRef]
24. Álvarez, A.H.; Estrada-Chávez, C.; Flores-Valdez, M.A. Molecular Findings and Approaches Spotlighting *Mycobacterium bovis* Persistence in Cattle. *Vet. Res.* **2009**, *40*, 22. [CrossRef] [PubMed]
25. Pollock, J.M.; Neill, S.D. *Mycobacterium bovis* Infection and Tuberculosis in Cattle. *Vet. J.* **2002**, *163*, 115–127. [CrossRef] [PubMed]
26. Alvarez, A.H.; Gutiérrez-Ortega, A.; Gómez-Entzin, V.; Pérez-Mayorga, G.; Naranjo-Bastién, J.; González-Martínez, V.; Milián-Suazo, F.; Martínez-Velázquez, M.; Herrera-Rodríguez, S.; Hinojoza-Loza, E. Assessment of Antigenic Supplementation of Bovine Purified Protein Derivative for Diagnosis of Subclinical Infection with *Mycobacterium bovis* in Cattle. *Microb. Pathog.* **2017**, *108*, 114–121. [CrossRef] [PubMed]
27. García, J.S.Y.; Bigi, M.M.; Klepp, L.I.; García, E.A.; Blanco, F.C.; Bigi, F. Does *Mycobacterium bovis* Persist in Cattle in a Non-Replicative Latent State as *Mycobacterium tuberculosis* in Human Beings? *Vet. Microbiol.* **2020**, *247*, 108758. [CrossRef] [PubMed]
28. Mukundan, H.; Chambers, M.; Waters, R.; Larsen, M. *Tuberculosis, Leprosy and Mycobacterial Diseases of Man and Animals: The Many Hosts of Mycobacteria*; CABI: London, UK, 2015. [CrossRef]
29. Brosch, R.; Gordon, S.V.; Marmiesse, M.; Brodin, P.; Buchrieser, C.; Eiglmeier, K.; Garnier, T.; Gutierrez, C.; Hewinson, G.; Kremer, K.; et al. A New Evolutionary Scenario for the *Mycobacterium tuberculosis* Complex. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 3684–3689. [CrossRef]

30. Niroula, N.; Lim, Z.L.; Walker, S.; Huang, Y.; Gerdts, V.; Zriba, S.; Drever, K.; Chen, J.M. Domestic Pigs Experimentally Infected with *Mycobacterium bovis* and *Mycobacterium tuberculosis* Exhibit Different Disease Outcomes. *Tuberculosis* **2022**, *133*, 102167. [CrossRef]
31. Villarreal-Ramos, B.; Berg, S.; Whelan, A.; Holbert, S.; Carreras, F.; Salguero, F.J.; Khatri, B.L.; Malone, K.; Rue-Albrecht, K.; Shaughnessy, R.; et al. Experimental Infection of Cattle with *Mycobacterium tuberculosis* Isolates Shows the Attenuation of the Human Tubercle Bacillus for Cattle. *Sci. Rep.* **2018**, *8*, 894. [CrossRef]
32. Barry, C.E.; Boshoff, H.; Dartois, V.; Dick, T.; Ehrt, S.; Flynn, J.; Schnappinger, D.; Wilkinson, R.J.; Young, D. The Spectrum of Latent Tuberculosis: Rethinking the Goals of Prophylaxis. *Nat. Rev. Microbiol.* **2009**, *7*, 845–855. [CrossRef]
33. Jenkins, H.E.; Woodroffe, R.; Donnelly, C.A.; Cox, D.R.; Johnston, W.T.; Bourne, F.J.; Cheeseman, C.L.; Clifton-Hadley, R.S.; Gettinby, G.; Gilks, P.; et al. Effects of Culling on Spatial Associations of *Mycobacterium bovis* Infections in Badgers and Cattle. *J. Appl. Ecol.* **2007**, *44*, 897–908. [CrossRef]
34. Van Tonder, A.J.; Thornton, M.J.; Conlan, A.J.K.; Jolley, K.A.; Goolding, L.; Mitchell, A.P.; Dale, J.; Palkopoulou, E.; Hogarth, P.J.; Hewinson, R.G.; et al. Inferring *Mycobacterium bovis* Transmission between Cattle and Badgers Using Isolates from the Randomised Badger Culling Trial. *PLoS Pathog.* **2021**, *17*, e1010075. [CrossRef] [PubMed]
35. Gormley, E.; Corner, L.A.L. Wild Animal Tuberculosis: Stakeholder Value Systems and Management of Disease. *Front. Vet. Sci.* **2018**, *5*, 327. [CrossRef] [PubMed]
36. Smith, R.L.; Tauer, L.W.; Schukken, Y.H.; Lu, Z.; Grohn, Y.T. Minimization of Bovine Tuberculosis Control Costs in US Dairy Herds. *Prev. Vet. Med.* **2013**, *112*, 266–275. [CrossRef]
37. Karolemeas, K.; de la Rua-Domenech, R.; Cooper, R.; Goodchild, A.V.; Clifton-Hadley, R.S.; Conlan, A.J.K.; Mitchell, A.P.; Hewinson, R.G.; Donnelly, C.A.; Wood, J.L.N.; et al. Estimation of the Relative Sensitivity of the Comparative Tuberculin Skin Test in Tuberculous Cattle Herds Subjected to Depopulation. *PLoS ONE* **2012**, *7*, e43217. [CrossRef]
38. Smith, R.L.; YH, S.; Lu, Z.; RM, M.; YT, G. Development of a Model to Simulate Infection Dynamics of *Mycobacterium bovis* in Cattle Herds in the United States. *J. Am. Vet. Med. Assoc.* **2013**, *243*, 411–423. [CrossRef]
39. Miller, M.A.; Buss, P.; Parsons, S.D.C.; Roos, E.; Chileshe, J.; Goosen, W.J.; van Schalkwyk, L.; de Klerk-Lorist, L.M.; Hofmeyr, M.; Hausler, G.; et al. Conservation of White Rhinoceroses Threatened by Bovine Tuberculosis, South Africa, 2016–2017. *Emerg. Infect. Dis.* **2018**, *24*, 2373–2375. [CrossRef] [PubMed]
40. Michel, A.L.; Bengis, R.G.; Keet, D.F.; Hofmeyr, M.; De Klerk, L.M.; Cross, P.C.; Jolles, A.E.; Cooper, D.; Whyte, I.J.; Buss, P.; et al. Wildlife Tuberculosis in South African Conservation Areas: Implications and Challenges. *Vet. Microbiol.* **2006**, *112*, 91–100. [CrossRef]
41. Gompo, T.R.; Shrestha, A.; Ranjit, E.; Gautam, B.; Ale, K.; Shrestha, S.; Bhatta, D.D. Risk Factors of Tuberculosis in Human and Its Association with Cattle TB in Nepal: A One Health Approach. *One Health* **2020**, *10*, 100156. [CrossRef]
42. Silva, M.R.; Rocha, A.D.S.; Araújo, F.R.; Fonseca-Júnior, A.A.; de Alencar, A.P.; Suffys, P.N.; da Costa, R.R.; Moreira, M.A.S.; Guimarães, M.D.C. Risk Factors for Human *Mycobacterium bovis* Infections in an Urban Area of Brazil. *Mem. Inst. Oswaldo Cruz* **2018**, *113*, e170445. [CrossRef]
43. Sichewo, P.R.; Michel, A.L.; Musoke, J.; Etter, E.M.C. Risk Factors for Zoonotic Tuberculosis at the Wildlife–Livestock–Human Interface in South Africa. *Pathogens* **2019**, *8*, 101. [CrossRef]
44. Bernitz, N.; Clarke, C.; Roos, E.O.; Goosen, W.J.; Cooper, D.; van Helden, P.D.; Parsons, S.D.C.; Miller, M.A. Detection of *Mycobacterium bovis* Infection in African Buffaloes (*Syncerus caffer)* Using QuantiFERON®-TB Gold (QFT) Tubes and the Qiagen Cattletype® IFN-Gamma ELISA. *Vet. Immunol. Immunopathol.* **2018**, *196*, 48–52. [CrossRef] [PubMed]
45. Clarke, C.; Cooper, D.; Goosen, W.J.; McFadyen, R.; Warren, R.M.; van Helden, P.D.; Parsons, S.D.C.; Miller, M.A. Antigen-Specific Interferon-Gamma Release Is Decreased Following the Single Intradermal Comparative Cervical Skin Test in African Buffaloes (*Syncerus caffer*). *Vet. Immunol. Immunopathol.* **2018**, *201*, 12–15. [CrossRef]
46. Miller, M.; Buss, P.; Hofmeyr, J.; Olea-Popelka, F.; Parsons, S.; van Helden, P. Antemortem Diagnosis of *Mycobacterium bovis* Infection in Free-Ranging African Lions (Panthera Leo) and Implications for Transmission. *J. Wildl. Dis.* **2015**, *51*, 493–497. [CrossRef] [PubMed]
47. Van Der Merwe, P.; Saayman, M. Determining the Economic Value of Game Farm Tourism. *Koedoe* **2003**, *46*, 103–112. [CrossRef]
48. Herrera, M.; Vera, C.; Keynan, Y.; Rueda, Z.V. Gaps in Study Design for Immune Parameter Research for Latent Tuberculosis Infection: A Systematic Review. *J. Immunol. Res.* **2020**, *2020*, 8074183. [CrossRef]
49. Miller, M. Tuberculosis in South African Wildlife: Why Is It Important? 2015. Available online: http://www.sun.ac.za/english/Inaugurallectures/Inaugurallectures/InauguralLectureProfMiller.pdf (accessed on 17 January 2019).
50. Siddique, A.B.; Hussain, R.; Jamal, A.; Hossain, M.B.; Ahmad, Z.; Mansoor, M.K.; Khan, I.; Zahra, K.; Khan, A. Histopathological Investigations and Molecular Confirmation Reveal *Mycobacterium bovis* in One-Horned Rhinoceros (Rhinoceros Unicorns). *BioMed Res. Int.* **2022**, *2022*, 5816986. [CrossRef]
51. Alvarez, A.H. Revisiting Tuberculosis Screening: An Insight to Complementary Diagnosis and Prospective Molecular Approaches for the Recognition of the Dormant TB Infection in Human and Cattle Hosts. *Microbiol. Res.* **2021**, *252*, 126853. [CrossRef] [PubMed]
52. Lopes, B.C.; dos Reis, E.M.; de Bitencourt, F.B.R.; Loiko, M.R.; Bezerra, A.V.A.; Bueno, T.S.; Lape, I.T.; Cerva, C.; Coppola, M.D.M.; Rodrigues, R.O.; et al. A Molecular Strategy to Optimize Bovine Tuberculosis Post-Mortem Diagnosis and the Exposure to *Mycobacterium tuberculosis* Variant Bovis. *Mol. Biol. Rep.* **2020**, *47*, 7291–7296. [CrossRef]

53. Meurens, F.; Dunoyer, C.; Fourichon, C.; Gerdts, V.; Haddad, N.; Kortekaas, J.; Lewandowska, M.; Monchatre-Leroy, E.; Summerfield, A.; Wichgers Schreur, P.J.; et al. Animal Board Invited Review: Risks of Zoonotic Disease Emergence at the Interface of Wildlife and Livestock Systems. *Animal* **2021**, *15*, 100241. [CrossRef]
54. Odoi, A.; Chavez-Lindell, T.L.; Moncayo, A.L.; Fernanda, M.; Veloz, V. An Exploratory Assessment of Human and Animal Health Concerns of Smallholder Farmers in Rural Communities of Chimborazo, Ecuador. *PeerJ* **2022**, *9*, e12208. [CrossRef]
55. Hlokwe, T.M.; Jenkins, A.O.; Streicher, E.M.; Venter, E.H.; Cooper, D.; Godfroid, J.; Michel, A.L. Molecular Characterisation of *Mycobacterium bovis* Isolated from African Buffaloes (Syncerus Caffer) in Hluhluwe-IMfolozi Park in KwaZulu-Natal, South Africa. *Onderstepoort J. Vet. Res.* **2011**, *78*, 6. [CrossRef] [PubMed]
56. Roug, A.; Muse, E.A.; Clifford, D.L.; Paul, G.; Mpanduji, D.; Makingi, G.; Magesa, W.; Josephat, E.; Mazet, J.; Bird, B.; et al. Health of African Buffalos (*Syncerus caffer*) in Ruaha National Park, Tanzania. *J. Wildl. Dis.* **2020**, *56*, 495–498. [CrossRef]
57. Shah, Y.; Paudel, S. Protect Elephants from Tuberculosis. *Science* **2021**, *374*, 832–833. [CrossRef] [PubMed]
58. Miller, M.A.; Finnegan, M.; Storms, T.; Garner, M.; Lyashchenko, K.P. Outbreak of *Mycobacterium tuberculosis* in a Herd of Captive Asian Elephants (*Elephas maximus*): Antemortem Diagnosis, Treatment, and Lessons Learned. *J. Zoo Wildl. Med.* **2018**, *49*, 748–754. [CrossRef] [PubMed]
59. Miller, M.A.; Hogan, J.N.; Meehan, C.L. Housing and Demographic Risk Factors Impacting Foot and Musculoskeletal Health in African Elephants [*Loxodonta africana*] and Asian Elephants [Elephas Maximus] in North American Zoos. *PLoS ONE* **2016**, *11*, e0155223. [CrossRef]
60. Glaeser, S.S.; Edwards, K.L.; Paris, S.; Scarlata, C.; Lee, B.; Wielebnowski, N.; Finnell, S.; Somgird, C.; Brown, J.L. Characterization of Longitudinal Testosterone, Cortisol, and Musth in Male Asian Elephants (*Elephas maximus*), Effects of Aging, and Adrenal Responses to Social Changes and Health Events. *Animals* **2022**, *12*, 1332. [CrossRef] [PubMed]
61. Ruetten, M.; Steinmetz, H.W.; Thiersch, M.; Kik, M.; Vaughan, L.; Altamura, S.; Muckenthaler, M.U.; Gassmann, M. Iron Regulation in Elderly Asian Elephants (*Elephas maximus*) Chronically Infected With *Mycobacterium tuberculosis*. *Front. Vet. Sci.* **2020**, *7*, 596379. [CrossRef]
62. Mikota, S.K.; Gairhe, K.; Giri, K.; Hamilton, K.; Miller, M.; Paudel, S.; Lyashchenko, K.; Larsen, R.S.; Payeur, J.B.; Waters, W.R.; et al. Tuberculosis Surveillance of Elephants (*Elephas maximus*) in Nepal at the Captive-Wild Interface. *Eur. J. Wildl. Res.* **2015**, *61*, 221–229. [CrossRef]
63. Katale, B.Z.; Mbugi, E.V.; Kendal, S.; Fyumagwa, R.D.; Kibiki, G.S.; Godfrey-Faussett, P.; Keyyu, J.D.; van Helden, P.; Matee, M.I. Bovine Tuberculosis at the Human-Livestock-Wildlife Interface: Is It a Public Health Problem in Tanzania?: A Review. *Onderstepoort J. Vet. Res.* **2012**, *79*, 8. [CrossRef] [PubMed]
64. Ayele, W.; Neill, S.; Zinsstag, J.; Weiss, M.; Pavlik, I. Bovine Tuberculosis: An Old Disease but a New Threat to Africa. *Int. J. Tuberc. Lung Dis.* **2004**, *8*, 924–937. [CrossRef]
65. Kaneene, J.B.; Miller, R.; de Kantor, I.N.; Thoen, C.O. Tuberculosis in Wild Animals. *Int. J. Tuberc. Lung Dis.* **2010**, *14*, 1508–1512. [PubMed]
66. Fitzgerald, S.D.; Kaneene, J.B. Wildlife Reservoirs of Bovine Tuberculosis Worldwide: Hosts, Pathology, Surveillance, and Control. *Vet. Pathol.* **2013**, *50*, 488–499. [CrossRef]
67. Goodchild, A.V.; Clifton-Hadley, R.S. Cattle-to-Cattle Transmission of *Mycobacterium bovis*. *Tuberculosis* **2001**, *81*, 23–41. [CrossRef] [PubMed]
68. Sanou, A.; Tarnagda, Z.; Kanyala, E.; Zingué, D.; Nouctara, M.; Ganamé, Z.; Combary, A.; Hien, H.; Dembele, M.; Kabore, A.; et al. *Mycobacterium bovis* in Burkina Faso: Epidemiologic and Genetic Links between Human and Cattle Isolates. *PLoS Negl. Trop. Dis.* **2014**, *8*, 3142. [CrossRef] [PubMed]
69. Neill, S.D.; Cassidy, J.; Hanna, J.; Mackie, D.P.; Pollock, J.M.; Clements, A.; Walton, E.; Bryson, D.G. Detection of *Mycobacterium bovis* Infection in Skin Test-Negative Cattle with an Assay for Bovine Interferon-Gamma. *Vet. Rec.* **1994**, *135*, 134–135. [CrossRef]
70. De Vos, V.; Bengis, R.G.; Kriek, N.P.; Michel, A.; Keet, D.F.; Raath, J.P.; Huchzermeyer, H.F. The Epidemiology of Tuberculosis in Free-Ranging African Buffalo (*Syncerus caffer*) in the Kruger National Park, South Africa. *Onderstepoort J. Vet. Res.* **2001**, *68*, 119–130.
71. Keet, D.F.; Kriek, N.P.J.; Bengis, R.G.; Grobler, D.G.; Michel, A. The Rise and Fall of Tuberculosis in a Free-Ranging Chacma Baboon Troop in the Kruger National Park. *Onderstepoort J. Vet. Res.* **2000**, *67*, 115–122.
72. Keet, D.F.; Kriek, N.P.J.; Bengis, R.G.; Michel, A.L. Tuberculosis in Kudus (*Tragelaphus strepsiceros*) in the Kruger National Park. *Onderstepoort J. Vet. Res.* **2001**, *68*, 225–230.
73. Paine, R.; Martinaglia, G. Tuberculosis in Wild Buck Living Under Natural Conditions. *J. Comp. Pathol. Ther.* **1929**, *42*, 1–8. [CrossRef]
74. Goosen, W.J.; Kleynhans, L.; Kerr, T.J.; van Helden, P.D.; Buss, P.; Warren, R.M.; Miller, M.A. Improved Detection of *Mycobacterium tuberculosis* and M. Bovis in African Wildlife Samples Using Cationic Peptide Decontamination and Mycobacterial Culture Supplementation. *J. Vet. Diagnostic Investig.* **2022**, *34*, 61–67. [CrossRef]
75. Hlokwe, T.M.; Id, O.; Article, O. First Detection of *Mycobacterium bovis* Infection in Giraffe (*Giraffa camelopardalis*) in the Greater Kruger National Park Complex: Role and Implications. *Transbound Emerg. Dis.* **2019**, *66*, 2264–2270. [CrossRef]
76. Gavier-Widen, D.; Chambers, M.A.; Palmer, N.; Newell, D.G.; Hewinson, R.G. Pathology of Natural *Mycobacterium bovis* Infection in European Badgers (*Meles meles*) and Its Relationship with Bacterial Excretion. *Vet. Rec.* **2001**, *148*, 299–304. [CrossRef] [PubMed]

77. Martin, L.E.R.; Byrne, A.W.; O'Keeffe, J.; Miller, M.A.; Olea-Popelka, F.J. Weather Influences Trapping Success for Tuberculosis Management in European Badgers (*Meles meles*). *Eur. J. Wildl. Res.* **2017**, *63*, 30. [CrossRef]
78. Jolma, E.R.; Delahay, R.J.; Smith, F.; Drewe, J.A. Serologic Responses Correlate with Current but Not Future Bacterial Shedding in Badgers Naturally Infected with *Mycobacterium bovis*. *Transbound. Emerg. Dis.* **2021**, *69*, 1922–1932. [CrossRef] [PubMed]
79. Infantes-Lorenzo, J.A.; Dave, D.; Moreno, I.; Anderson, P.; Lesellier, S.; Gormley, E.; Dominguez, L.; Balseiro, A.; Gortázar, C.; Dominguez, M.; et al. New Serological Platform for Detecting Antibodies against *Mycobacterium tuberculosis* Complex in European Badgers. *Vet. Med. Sci.* **2019**, *5*, 61–69. [CrossRef]
80. Katale, B.Z.; Mbugi, E.V.; Siame, K.K.; Keyyu, J.D.; Kendall, S.; Kazwala, R.R.; Dockrell, H.M.; Fyumagwa, R.D.; Michel, A.L.; Rweyemamu, M.; et al. Isolation and Potential for Transmission of *Mycobacterium bovis* at Human–Livestock–Wildlife Interface of the Serengeti Ecosystem, Northern Tanzania. *Transbound. Emerg. Dis.* **2017**, *64*, 815–825. [CrossRef]
81. Michel, A.L.; Coetzee, M.L.; Keet, D.F.; Maré, L.; Warren, R.; Cooper, D.; Bengis, R.G.; Kremer, K.; van Helden, P. Molecular Epidemiology of *Mycobacterium bovis* Isolates from Free-Ranging Wildlife in South African Game Reserves. *Vet. Microbiol.* **2009**, *133*, 335–343. [CrossRef]
82. Bouts, T.; Vordermeier, M.; Flach, E.; Routh, A. Positive Skin and Serologic Test Results of Diagnostic Assays for Bovine Tuberculosis and Subsequent Isolation of *Mycobacterium interjectum* in a Pygmy Hippopotamus (*Hexaprotodon liberiensis*). *J. Zoo Wildl. Med.* **2009**, *40*, 536–542. [CrossRef]
83. Kerr, T.J.; Goosen, W.J.; Gumbo, R.; de Klerk-Lorist, L.M.; Pretorius, O.; Buss, P.E.; Kleynhans, L.; Lyashchenko, K.P.; Warren, R.M.; van Helden, P.D.; et al. Diagnosis of *Mycobacterium bovis* Infection in Free-Ranging Common Hippopotamus (*Hippopotamus amphibius*). *Transbound. Emerg. Dis.* **2022**, *69*, 378–384. [CrossRef]
84. De Vos, V.; McCully, R.M.; van Niekerk, C.A.W.J. Mycobacteriosis in the Kruger National Park. *Koedoe* **1977**, *20*, a928. [CrossRef]
85. Tanner, M.; Michel, A.L. Investigation of the Viability of *Mycobacterium bovis* under Different Environmental Conditions in the Kruger National Park. *Onderstepoort J. Vet. Res.* **1999**, *66*, 185–190.
86. Hlokwe, T.M.; Mogano, R.M. Utility of Xpert® MTB/RIF Ultra Assay in the Rapid Diagnosis of Bovine Tuberculosis in Wildlife and Livestock Animals from South Africa. *Prev. Vet. Med.* **2020**, *177*, 104980. [CrossRef]
87. Palmer, M.V. *Mycobacterium bovis*: Characteristics of Wildlife Reservoir Hosts. *Transbound. Emerg. Dis.* **2013**, *60* (Suppl. S1), 1–13. [CrossRef]
88. Miller, M.A.; Buss, P.; Sylvester, T.T.; Lyashchenko, K.P.; Deklerk-Lorist, L.-M.; Bengis, R.; Hofmeyr, M.; Hofmeyr, J.; Mathebula, N.; Hausler, G.; et al. *Mycobacterium bovis* in Free-Ranging Lions (*Panthera leo*)—Evaluation of Serological and Tuberculin Skin Tests for Detection of Infection and Disease. *J. Zoo Wildl. Med.* **2019**, *50*, 7. [CrossRef] [PubMed]
89. Gumbo, R.; Sylvester, T.T.; Goosen, W.J.; Buss, P.E.; de Klerk-Lorist, L.-M.; van Schalkwyk, O.L.; McCall, A.; Warren, R.M.; van Helden, P.D.; Miller, M.A.; et al. Adaptation and Diagnostic Potential of a Commercial Cat Interferon Gamma Release Assay for the Detection of *Mycobacterium bovis* Infection in African Lions (*Panthera leo*). *Pathogens* **2022**, *11*, 765. [CrossRef] [PubMed]
90. Brüns, A.C.; Brüns, B.; Tanner, M.; Williams, M.C.; Botha, L.; O'brien, A.; Fosgate, G.T.; Van Helden, P.D.; Clarke, J.; Michel, A.L. Diagnosis and Implications of *Mycobacterium bovis* Infection in Banded Mongooses (*Mungos mungo*) in the Kruger National Park, South Africa. *J. Wildl. Dis.* **2017**, *53*, 19–29. [CrossRef]
91. Palmer, M.V.; Thacker, T.C.; Rabideau, M.M.; Jones, G.J.; Kanipe, C.; Vordermeier, H.M.; Waters, W.R. Veterinary Immunology and Immunopathology Biomarkers of Cell-Mediated Immunity to Bovine Tuberculosis. *Vet. Immunol. Immunopathol.* **2020**, *220*, 109988. [CrossRef]
92. Thomas, J.; Balseiro, A.; Gortázar, C.; Risalde, M.A. Diagnosis of Tuberculosis in Wildlife: A Systematic Review. *Vet. Res.* **2021**, *52*, 31. [CrossRef]
93. Miller, M.; Chavey, P.S.; Hofmeyr, J.; Mathebula, N.; Doering, A.; Buss, P.; Olea-Popelka, F. Evaluation of Serum Ferritin and Serum Iron in Free-Ranging Black Rhinoceros (*Diceros bicornis*) as a Tool to Understand Factors Affecting Iron-Overload Disorder. *J. Zoo Wildl. Med.* **2016**, *47*, 820–826. [CrossRef]
94. Miller, M.A.; Greenwald, R.; Lyashchenko, K.P. Potential for Serodiagnosis of Tuberculosis in Black Rhinoceros (*Diceros bicornis*). *J. Zoo Wildl. Med.* **2015**, *46*, 100–104. [CrossRef]
95. Dwyer, R.A.; Witte, C.; Buss, P.; Goosen, W.J.; Miller, M.; Caron, A. Epidemiology of Tuberculosis in Multi-Host Wildlife Systems: Implications for Black (*Diceros bicornis*) and White (*Ceratotherium simum*) Rhinoceros. *Front. Vet. Sci.* **2020**, *7*, 580476. [CrossRef] [PubMed]
96. Richomme, C.; Réveillaud, E.; Moyen, J.-L.; Sabatier, P.; De Cruz, K.; Michelet, L.; Boschiroli, M.L. *Mycobacterium bovis* Infection in Red Foxes in Four Animal Tuberculosis Endemic Areas in France. *Microorganisms* **2020**, *8*, 1070. [CrossRef]
97. Roos, E.O.; Buss, P.; de Klerk-Lorist, L.M.; Hewlett, J.; Hausler, G.A.; Rossouw, L.; McCall, A.J.; Cooper, D.; van Helden, P.D.; Parsons, S.D.C.; et al. Test Performance of Three Serological Assays for the Detection of *Mycobacterium bovis* Infection in Common Warthogs (*Phacochoerus africanus*). *Vet. Immunol. Immunopathol.* **2016**, *182*, 79–84. [CrossRef] [PubMed]
98. Roos, E.O.; Olea-Popelka, F.; Buss, P.; Hausler, G.A.; Warren, R.; Van Helden, P.D.; Parsons, S.D.C.; De Klerk-Lorist, L.M.; Miller, M.A. Measuring Antigen-Specific Responses in *Mycobacterium bovis*-Infected Warthogs (*Phacochoerus africanus*) Using the Intradermal Tuberculin Test. *BMC Vet. Res.* **2018**, *14*, 360. [CrossRef] [PubMed]
99. Roos, E.O.; Olea-Popelka, F.; Buss, P.; de Klerk-Lorist, L.M.; Cooper, D.; van Helden, P.D.; Parsons, S.D.C.; Miller, M.A. Seroprevalence of *Mycobacterium bovis* Infection in Warthogs (*Phacochoerus africanus*) in Bovine Tuberculosis-Endemic Regions of South Africa. *Transbound. Emerg. Dis.* **2018**, *65*, 1182–1189. [CrossRef]

100. Campana, M.G.; Parker, L.D.; Hawkins, M.T.R.; Young, H.S.; Helgen, K.M.; Szykman Gunther, M.; Woodroffe, R.; Maldonado, J.E.; Fleischer, R.C. Genome Sequence, Population History, and Pelage Genetics of the Endangered African Wild Dog (*Lycaon pictus*). *BMC Genom.* **2016**, *17*, 1. [CrossRef] [PubMed]
101. Meiring, C.; Schurz, H.; van Helden, P.; Hoal, E.; Tromp, G.; Kinnear, C.; Kleynhans, L.; Glanzmann, B.; van Schalkwyk, L.; Miller, M.; et al. African Wild Dogs (*Lycaon pictus*) from the Kruger National Park, South Africa Are Currently Not Inbred but Have Low Genomic Diversity. *Sci. Rep.* **2022**, *12*, 14979. [CrossRef]
102. Overton, J.M.C.; Elizalde Castells, D.; Figueira Fernandes Elizalde, S.R.; Valério, H.M.; Alexandre Zumbo, M.N.; Groom, R.J.; Durant, S.M. Endangered African Wild Dogs (*Lycaon pictus* Temm.) in Angola: Filling a 50-Year Gap of Knowledge with Findings from Two National Parks. *Afr. J. Ecol.* **2020**, *58*, 582–587. [CrossRef]
103. Higgitt, R.L.; Van Schalkwyk, O.L.; De Klerk-Lorist, L.M.; Buss, P.E.; Caldwell, P.; Rossouw, L.; Manamela, T.; Hausler, G.A.; Hewlett, J.; Mitchell, E.P.; et al. *Mycobacterium bovis* Infection in African Wild Dogs, Kruger National Park, South Africa. *Emerg. Infect. Dis.* **2019**, *25*, 1425–1427. [CrossRef]
104. Kock, R.A.; Woodford, M.H.; Rossiter, P.B. Disease Risks Associated with the Translocation of Wildlife. *OIE Rev. Sci. Tech.* **2010**, *29*, 329–350. [CrossRef]
105. Hlokwe, T.M.; van Helden, P.; Michel, A.L. Evidence of Increasing Intra and Inter-Species Transmission of *Mycobacterium bovis* in South Africa: Are We Losing the Battle? *Prev. Vet. Med.* **2014**, *115*, 10–17. [CrossRef] [PubMed]
106. Miller, M.; Michel, A.; van Helden, P.; Buss, P. Tuberculosis in Rhinoceros: An Underrecognized Threat? *Transbound. Emerg. Dis.* **2017**, *64*, 1071–1078. [CrossRef] [PubMed]
107. Monies, B.; de la Rua, R.; Jahans, K. Bovine Tuberculosis in Cats. *Vet. Rec.* **2006**, *158*, 490–491. [CrossRef] [PubMed]
108. Srivastava, K.; Chauhan, D.S.; Gupta, P.; Singh, H.B.; Sharma, V.D.; Yadav, V.S.; Sreekumaran; Thakral, S.S.; Dharamdheeran, J.S.; Nigam, P.; et al. Isolation of *Mycobacterium bovis* & *Mycobacterium tuberculosis* from Cattle of Some Farms in North India-Possible Relevance in Human Health. *Indian J. Med. Res.* **2008**, *128*, 26–31.
109. Sweetline Anne, N.; Ronald, B.S.M.; Kumar, T.M.A.S.; Kannan, P.; Thangavelu, A. Molecular Identification of *Mycobacterium tuberculosis* in Cattle. *Vet. Microbiol.* **2017**, *198*, 81–87. [CrossRef]
110. Ghodbane, R.; Drancourt, M. Non-Human Sources of *Mycobacterium tuberculosis*. *Tuberculosis* **2013**, *93*, 589–595. [CrossRef]
111. Ravindran, R.; Krishnan, V.V.; Dhawan, R.; Wunderlich, M.L.; Lerche, N.W.; Flynn, J.L.; Luciw, P.A.; Khan, I.H. Plasma Antibody Profiles in Non-Human Primate Tuberculosis. *J. Med. Primatol.* **2014**, *43*, 59–71. [CrossRef]
112. Parsons, S.D.C.; Warren, R.M.; Ottenhoff, T.H.M.; Gey van Pittius, N.C.; van Helden, P.D. Detection of *Mycobacterium tuberculosis* Infection in Dogs in a High-Risk Setting. *Res. Vet. Sci.* **2012**, *92*, 414–419. [CrossRef]
113. Haydock, L.A.J.; Abrams-Ogg, A.C.G.; Weese, J.S.; Goldstein, M.R.; Clifford, A.B.; Sebastian, A.; Rea, E.H.; Jamieson, F.B.; Duncan, C.; Andrievskaia, O.; et al. Diagnostic and Public Health Investigation of *Mycobacterium tuberculosis* Infection in a Dog in Ontario, Canada. *J. Vet. Diagn. Investig.* **2022**, *34*, 292–297. [CrossRef]
114. Marfil, M.J.; Barandiaran, S.; Zumárraga, M.J.; Germani, L.; Faccini, T.; Linares, M.; Capra, S.; Gramajo, L.; Martínez Vivot, M.; Falzoni, E. *Mycobacterium tuberculosis* Infection in a Free-Ranging Urban Dog from Argentina. *Vet. Res. Commun.* **2022**, *46*, 781–788. [CrossRef]
115. Une, Y.; Mori, T. Tuberculosis as a Zoonosis from a Veterinary Perspective. *Comp. Immunol. Microbiol. Infect. Dis.* **2007**, *30*, 415–425. [CrossRef] [PubMed]
116. Montali, R.J.; Mikota, S.K.; Cheng, L.I. *Mycobaterium tuberculosis* in Zoo and Wildlife Species. *Sci. Tech. Rev. Int. Off. Epizoot.* **2001**, *20*, 291–303. [CrossRef] [PubMed]
117. Rosen, L.E.; Hanyire, T.G.; Dawson, J.; Foggin, C.M.; Michel, A.L.; Huyvaert, K.P.; Miller, M.A.; Olea-Popelka, F.J. Tuberculosis Serosurveillance and Management Practices of Captive African Elephants (*Loxodonta africana*) in the Kavango-Zambezi Transfrontier Conservation Area. *Transbound. Emerg. Dis.* **2018**, *65*, e344–e354. [CrossRef] [PubMed]
118. Landolfi, J.A.; Terio, K.A.; Miller, M.; Junecko, B.F.; Reinhart, T. Pulmonary Tuberculosis in Asian Elephants (*Elephas maximus*): Histologic Lesions with Correlation to Local Immune Responses. *Vet. Pathol.* **2015**, *52*, 535–542. [CrossRef] [PubMed]
119. Sarad, P.; Tsubota, T. Tuberculosis in Elephants: A Zoonotic Disease at the Human-Elephant Interface. *Japanese J. Zoo Wildl. Med.* **2016**, *21*, 65–69. [CrossRef]
120. Bezos, J.; Casal, C.; Díez-Delgado, I.; Romero, B.; Liandris, E.; Álvarez, J.; Sevilla, I.A.; de Juan, L.; Domínguez, L.; Gortázar, C. Goats Challenged with Different Members of the *Mycobacterium tuberculosis* Complex Display Different Clinical Pictures. *Vet. Immunol. Immunopathol.* **2015**, *167*, 185–189. [CrossRef]
121. Cadmus, S.I.B.; Jenkins, A.O.; Godfroid, J.; Osinusi, K.; Adewole, I.F.; Murphy, R.L.; Taiwo, B.O. *Mycobacterium tuberculosis* and *Mycobacterium africanum* in Stools from Children Attending an Immunization Clinic in Ibadan, Nigeria. *Int. J. Infect. Dis.* **2009**, *13*, 740–744. [CrossRef]
122. Silva, M.L.; Cá, B.; Osório, N.S.; Rodrigues, P.N.S.; Maceiras, A.R.; Saraiva, M. Tuberculosis Caused by *Mycobacterium africanum*: Knowns and Unknowns. *PLoS Pathog.* **2022**, *18*, e1010490. [CrossRef]
123. Gonzalo-Asensio, J.; Astarie-Dequeker, C.; Malaga, W.; Brosch, R.; Moreau, F.; Passemar, C.; Martin, C.; Laval, F.; Daffe, M.; Guilhot, C.; et al. Evolutionary History of Tuberculosis Shaped by Conserved Mutations in the PhoPR Virulence Regulator. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 11491–11496. [CrossRef]

124. Rahim, Z.; Möllers, M.; Te Koppele-Vije, A.; De Beer, J.; Zaman, K.; Matin, M.A.; Kamal, M.; Raquib, R.; Van Soolingen, D.; Baqi, M.A.; et al. Characterization of *Mycobacterium africanum* Subtype 1 among Cows in a Dairy Farm in Bangladesh Using Spoligotyping. *Southeast Asian J. Trop. Med. Public Health* **2007**, *38*, 706–713.
125. Gudan, A.; Artuković, B.; Cvetnić, Ž.; Špičić, S.; Beck, A.; Hohšteter, M.; Naglić, T.; Bata, I.; Grabarević, Ž. Disseminated Tuberculosis in Hyrax (*Procavia capensis*) Caused by *Mycobacterium africanum*. *J. Zoo Wildl. Med.* **2008**, *39*, 386–391. [CrossRef] [PubMed]
126. Cousins, D.V.; Bastida, R.; Cataldi, A.; Quse, V.; Redrobe, S.; Dow, S.; Duignan, P.; Murray, A.; Dupont, C.; Ahmed, N.; et al. Tuberculosis in Seals Caused by a Novel Member of the *Mycobacterium tuberculosis* Complex: *Mycobacterium pinnipedii* Sp. Nov. *Int. J. Syst. Evol. Microbiol.* **2003**, *53*, 1305–1314. [CrossRef]
127. Kiers, A.; Klarenbeek, A.; Mendelts, B.; Van Soolingen, D.; Koëter, G. Transmission of *Mycobacterium pinnipedii* to Humans in a Zoo with Marine Mammals. *Int. J. Tuberc. Lung Dis.* **2008**, *12*, 1469–1473. [PubMed]
128. Macedo, R.; Isidro, J.; Gomes, M.C.; Botelho, A.; Albuquerque, T.; Sogorb, A.; Bernardino, R.; Fernandes, T.L.; Mourato, T.; Durval, M.; et al. Animal-to-Human Transmission of *Mycobacterium pinnipedii*. *Eur. Respir. J.* **2020**, *56*, 2000371. [CrossRef]
129. Loeffler, S.H.; de Lisle, G.W.; Neill, M.A.; Collins, D.M.; Price-Carter, M.; Paterson, B.; Crews, K.B. The Seal Tuberculosis Agent, *Mycobacterium pinnipedii*, Infects Domestic Cattle in New Zealand: Epidemiologic Factors and DNA Strain Typing. *J. Wildl. Dis.* **2014**, *50*, 180–187. [CrossRef] [PubMed]
130. Aranaz, A.; Liebana, E.; Gomez-Mampaso, E.; Galán, J.C.; Cousins, D.; Ortega, A.; Blázquez, J.; Baquero, F.; Mateos, A.; Súarez, G.; et al. Mycobacterium tuberculosis Subsp. caprae subsp. nov.: A Taxonomic Study of a New Member of the Mycobacterium tuberculosis Complex Isolated from Goats in Spain. *Int. J. Syst. Bacteriol.* **1999**, *49*, 1263–1273. [CrossRef] [PubMed]
131. Gormley, E.; Corner, L.A.L.; Costello, E.; Rodriguez-Campos, S. Bacteriological Diagnosis and Molecular Strain Typing of *Mycobacterium bovis* and *Mycobacterium caprae*. *Res. Vet. Sci.* **2014**, *97*, S30–S43. [CrossRef]
132. Shrestha, A.; Picoy, J.; Torres, A.; Moore, D.A.; Gilman, R.H.; Coronel, J.; Grandjean, L. A Case Report of Transmission and Disease Caused by *Mycobacterium caprae* and *Mycobacterium bovis* in Lima, Peru. *BMC Infect. Dis.* **2021**, *21*, 4–9. [CrossRef]
133. Huitema, H.; Jaartsveld, F.H.J. *Mycobacterium microti* Infection in a Cat and Some Pigs. *Antonie Van Leeuwenhoek* **1967**, *33*, 209–212. [CrossRef]
134. Wells, A.Q.; Robb-Smith, A.H.T. Murine Type of Tubercle Bacillus (the Vole Acid-Fast Bacillus). 1946. Available online: https://agris.fao.org/agris-search/search.do?recordID=US201300343701 (accessed on 11 August 2022).
135. Van Soolingen, D.; Van Der Zanden, A.G.M.; De Haas, P.E.W.; Noordhoek, G.T.; Kiers, A.; Foudraine, N.A.; Portaels, F.; Kolk, A.H.J.; Kremer, K.; Van Embden, J.D.A. Diagnosis of *Mycobacterium microti* Infections among Humans by Using Novel Genetic Markers. *J. Clin. Microbiol.* **1998**, *36*, 1840–1845. [CrossRef]
136. van Ingen, J.; Brosch, R.; van Soolingen, D. Characterization of *Mycobacterium orygis*. *Emerg. Infect. Dis.* **2013**, *19*, 521–522. [CrossRef] [PubMed]
137. Van Soolingen, D.; De Haas, P.E.W.; Haagsma, J.; Eger, T.; Hermans, P.W.M.; Ritacco, V.; Alito, A.; Va Embdenl, J.D.A. Use of Various Genetic Markers in Differentiation of *Mycobacterium bovis* Strains from Animals and Humans and for Studying Epidemiology of Bovine Tuberculosis. *J. Clin. Microbiol.* **1994**, *32*, 2425–2433. [CrossRef] [PubMed]
138. Parsons, S.D.C. *Mycobacterium orygis*: A Zoonosis, Zooanthroponosis, or Both? *Lancet Microbe* **2020**, *1*, e240. [CrossRef]
139. Pfyffer, G.E.; Auckenthaler, R.; Van Embden, J.D.A.; Van Soolingen, D. *Mycobacterium canettii*, the Smooth Variant of *Mycobacterium tuberculosis*, Isolated from a Swiss Patient Exposed in Africa. *Emerg. Infect. Dis.* **1998**, *4*, 631–634. [CrossRef] [PubMed]
140. Van Soolingen, D.; Hoogenboezem, T.; De Haas, P.E.W.; Hermans, P.W.M.; Koedam, M.A.; Teppema, K.S.; Brennan, P.J.; Besra, G.S.; Portaels, F.; Top, J.; et al. A Novel Pathogenic Taxon of the *Mycobacterium tuberculosis* Complex, Canetti: Characterization of an Exceptional Isolate from Africa. *Int. J. Syst. Bacteriol.* **1997**, *47*, 1236–1245. [CrossRef] [PubMed]
141. Supply, P.; Brosch, R. The Biology and Epidemiology of *Mycobacterium canettii*. *Adv. Exp. Med. Biol.* **2017**, *1019*, 27–41. [CrossRef]
142. Alexander, K.A.; Laver, P.N.; Michel, A.L.; Williams, M.; van Helden, P.D.; Warren, R.M.; van Pittius, N.C.G. Novel *Mycobacterium tuberculosis* Complex Pathogen, M. Mungi. *Emerg. Infect. Dis.* **2010**, *16*, 1296–1299. [CrossRef]
143. Dippenaar, A.; Parsons, S.D.C.; Sampson, S.L.; Van Der Merwe, R.G.; Drewe, J.A.; Abdallah, A.M.; Siame, K.K.; Gey Van Pittius, N.C.; Van Helden, P.D.; Pain, A.; et al. Whole Genome Sequence Analysis of *Mycobacterium suricattae*. *Tuberculosis* **2015**, *95*, 682–688. [CrossRef]
144. Clarke, C.; Van Helden, P.; Miller, M.; Parsons, S. Animal-Adapted Members of the *Mycobacterium tuberculosis* Complex Endemic to the Southern African Subregion. *J. S. Afr. Vet. Assoc.* **2016**, *87*, 1322. [CrossRef]
145. Parsons, S.D.C.; Drewe, J.A.; van Pittius, N.C.G.; Warren, R.M.; van Helden, P.D. Novel Cause of Tuberculosis in Meerkats, South Africa. *Emerg. Infect. Dis.* **2013**, *19*, 2004–2007. [CrossRef]
146. Glaziou, P.; Floyd, K.; Raviglione, M.C. Global Epidemiology of Tuberculosis. *Semin. Respir. Crit. Care Med.* **2015**, *39*, 271–285. [CrossRef] [PubMed]
147. Morris, R.S.; Pfeiffer, D.U.; Jackson, R. The Epidemiology of *Mycobacterium bovis* Infections. *Vet. Microbiol.* **1994**, *40*, 153–177. [CrossRef]
148. Phipps, E.; McPhedran, K.; Edwards, D.; Russell, K.; O'Connor, C.M.; Gunn-Moore, D.A.; O'Halloran, C.; Roberts, T.; Morris, J. Bovine Tuberculosis in Working Foxhounds: Lessons Learned from a Complex Public Health Investigation. *Epidemiol. Infect.* **2019**, *147*, E24. [CrossRef] [PubMed]

149. Haddad, N.; Ostyn, A.; Karoui, C.; Masselot, M.; Thorel, M.F.; Hughes, S.L.; Inwald, J.; Hewinson, R.G.; Durand, B. Spoligotype Diversity of *Mycobacterium bovis* Strains Isolated in France from 1979 to 2000. *J. Clin. Microbiol.* **2001**, *39*, 3623–3632. [CrossRef] [PubMed]
150. Almaw, G.; Mihret, A.; Abebe, T.; Ameni, G.; Gumi, B.; Olani, A.; Tamiru, M.; Koran, T.; Aliy, A.; Sombo, M.; et al. Spoligotype Analysis of *Mycobacterium bovis* Isolates from Cattle and Assessment of Zoonotic TB Transmission among Individuals Working in Bovine TB- Infected Dairy Farms in Ethiopia. *Zoonoses Public Health* **2022**, *69*, 663–672. [CrossRef]
151. Branger, M.; Loux, V.; Cochard, T.; Boschiroli, M.L.; Biet, F.; Michelet, L. The Complete Genome Sequence of *Mycobacterium bovis* Mb3601, a SB0120 Spoligotype Strain Representative of a New Clonal Group. *Infect. Genet. Evol.* **2020**, *82*, 104309. [CrossRef]
152. Boniotti, M.B.; Goria, M.; Loda, D.; Garrone, A.; Benedetto, A.; Mondo, A.; Tisato, E.; Zanoni, M.; Zoppi, S.; Dondo, A.; et al. Molecular Typing of *Mycobacterium bovis* Strains Isolated in Italy from 2000 to 2006 and Evaluation of Variable-Number Tandem Repeats for Geographically Optimized Genotyping. *J. Clin. Microbiol.* **2009**, *47*, 636–644. [CrossRef]
153. Hlokwe, T.M.; Van Helden, P.; Michel, A. Evaluation of the Discriminatory Power of Variable Number of Tandem Repeat Typing of *Mycobacterium bovis* Isolates from Southern Africa. *Transbound. Emerg. Dis.* **2013**, *60* (Suppl. S1), 111–120. [CrossRef]
154. Amato, B.; Di Marco Lo Presti, V.; Gerace, E.; Capucchio, M.T.; Vitale, M.; Zanghì, P.; Pacciarini, M.L.; Marianelli, C.; Boniotti, M.B. 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. *Transbound. Emerg. Dis.* **2018**, *65*, e416–e424. [CrossRef]
155. Broeckl, S.; Krebs, S.; Varadharajan, A.; Straubinger, R.K.; Blum, H.; Buettner, M. Investigation of Intra-Herd Spread of *Mycobacterium caprae* in Cattle by Generation and Use of a Whole-Genome Sequence. *Vet. Res. Commun.* **2017**, *41*, 113–128. [CrossRef]
156. Orloski, K.; Robbe-Austerman, S.; Tod Stuber, B.H.; Schoenbaum, M. Whole Genome Sequencing of *Mycobacterium bovis* Isolated from Livestock in the United States, 1989–2018. *Front. Vet. Sci.* **2018**, *5*, 253. [CrossRef]
157. Valcheva, V.; Perea, C.; Savova-Lalkovska, T.; Dimitrova, A.; Radulski, L.; Mokrousov, I.; Marinov, K.; Najdenski, H.; Bonovska, M. *Mycobacterium bovis* and *Mycobacterium caprae* in Bulgaria: Insight into Transmission and Phylogeography Gained through Whole-Genome Sequencing. *BMC Vet. Res.* **2022**, *18*, 148. [CrossRef] [PubMed]
158. Sandoval-Azuara, S.E.; Muñiz-Salazar, R.; Perea-Jacobo, R.; Robbe-Austerman, S.; Perera-Ortiz, A.; López-Valencia, G.; Bravo, D.M.; Sanchez-Flores, A.; Miranda-Guzmán, D.; Flores-López, C.A.; et al. Whole Genome Sequencing of *Mycobacterium bovis* to Obtain Molecular Fingerprints in Human and Cattle Isolates from Baja California, Mexico. *Int. J. Infect. Dis.* **2017**, *63*, 48–56. [CrossRef] [PubMed]
159. Price-Carter, M.; Brauning, R.; de Lisle, G.W.; Livingstone, P.; Neill, M.; Sinclair, J.; Paterson, B.; Atkinson, G.; Knowles, G.; Crews, K.; et al. Whole Genome Sequencing for Determining the Source of *Mycobacterium bovis* Infections in Livestock Herds and Wildlife in New Zealand. *Front. Vet. Sci.* **2018**, *5*, 272. [CrossRef] [PubMed]
160. de la Rua-Domenech, R.; Goodchild, A.T.; Vordermeier, H.M.; Hewinson, R.G.; Christiansen, K.H.; Clifton-Hadley, R.S. Ante Mortem Diagnosis of Tuberculosis in Cattle: A Review of the Tuberculin Tests, γ-Interferon Assay and Other Ancillary Diagnostic Techniques. *Res. Vet. Sci.* **2006**, *81*, 190–210. [CrossRef]
161. Roos, E.O.; Olea-Popelka, F.; Buss, P.; de Klerk-Lorist, L.M.; Cooper, D.; Warren, R.M.; van Helden, P.D.; Parsons, S.D.C.; Miller, M.A. IP-10: A Potential Biomarker for Detection of *Mycobacterium bovis* Infection in Warthogs (*Phacochoerus africanus*). *Vet. Immunol. Immunopathol.* **2018**, *201*, 43–48. [CrossRef]
162. Roos, E.O. *Detection and Characterization of Mycobacterial Infections Occurring in Phacochoerus Africanus (Gmelin, 1788) (Common Warthog)*; Stellenbosch University: Stellenbosch, South Africa, 2018.
163. Majoor, C.J.; Magis-Escurra, C.; van Ingen, J.; Boeree, M.J.; van Soolingen, D. Epidemiology of *Mycobacterium bovis* Disease in Humans, The Netherlands, 1993–2007. *Emerg. Infect. Dis.* **2011**, *17*, 457–463. [CrossRef]
164. Rabaa, M.A.; Tue, N.T.; Phuc, T.M.; Carrique-Mas, J.; Saylors, K.; Cotten, M.; Bryant, J.E.; Nghia, H.D.T.; Van Cuong, N.; Pham, H.A.; et al. The Vietnam Initiative on Zoonotic Infections (VIZIONS): A Strategic Approach to Studying Emerging Zoonotic Infectious Diseases. *Ecohealth* **2015**, *12*, 726–735. [CrossRef]
165. Durr, P.A.; Hewinson, R.G.; Clifton-Hadley, R.S. Molecular Epidemiology of Bovine Tuberculosis. I. Mycobacterium bovis Genotyping. *Rev. Sci. Tech.* **2000**, *19*, 675–688. [CrossRef]
166. Mostowy, S.; Behr, M.A. Comparative Genomics in the Fight against Tuberculosis: Diagnostics, Epidemiology, and BCG Vaccination. *Am. J. Pharm.* **2002**, *2*, 189–196. [CrossRef]
167. Campbell, E.L.; Byrne, A.W.; Menzies, F.D.; Milne, G.; McBride, K.R.; McCormick, C.M.; Scantlebury, D.M.; Reid, N. Quantifying Intraherd Cattle Movement Metrics: Implications for Disease Transmission Risk. *Prev. Vet. Med.* **2020**, *185*, 106192. [CrossRef] [PubMed]
168. Ghebremariam, M.K.; Michel, A.L.; Vernooij, J.C.M.; Nielen, M.; Rutten, V.P.M.G. Prevalence of Bovine Tuberculosis in Cattle, Goats, and Camels of Traditional Livestock Raising Communities in Eritrea. *BMC Vet. Res.* **2018**, *14*, 73. [CrossRef]
169. O'Brien, D.J.; Schmitt, S.M.; Fierke, J.S.; Hogle, S.A.; Winterstein, S.R.; Cooley, T.M.; Moritz, W.E.; Diegel, K.L.; Fitzgerald, S.D.; Berry, D.E.; et al. Epidemiology of *Mycobacterium bovis* in Free-Ranging White-Tailed Deer, Michigan, USA, 1995–2000. *Prev. Vet. Med.* **2002**, *54*, 47–63. [CrossRef]

170. Zimpel, C.K.; Patané, J.S.L.; Guedes, A.C.P.; de Souza, R.F.; Silva-Pereira, T.T.; Camargo, N.C.S.; de Souza Filho, A.F.; Ikuta, C.Y.; Neto, J.S.F.; Setubal, J.C.; et al. Global Distribution and Evolution of *Mycobacterium bovis* Lineages. *Front. Microbiol.* **2020**, *11*, 843. [CrossRef] [PubMed]
171. Galagan, J.E. Genomic Insights into Tuberculosis. *Nat. Rev. Genet.* **2014**, *15*, 307–320. [CrossRef]
172. Coscolla, M.; Gagneux, S. Consequences of Genomic Diversity in *Mycobacterium tuberculosis*. *Semin. Immunol.* **2014**, *26*, 431–444. [CrossRef]
173. Otchere, I.D.; van Tonder, A.J.; Asante-Poku, A.; Sánchez-Busó, L.; Coscollá, M.; Osei-Wusu, S.; Asare, P.; Aboagye, S.Y.; Ekuban, S.A.; Yahayah, A.I.; et al. Molecular Epidemiology and Whole Genome Sequencing Analysis of Clinical *Mycobacterium bovis* from Ghana. *PLoS ONE* **2019**, *14*, e0209395. [CrossRef]
174. De Jong, B.C.; Adetifa, I.; Walther, B.; Hill, P.C.; Antonio, M.; Ota, M.; Adegbola, R.A. Differences between Tuberculosis Cases Infected with *Mycobacterium africanum*, West African Type 2, Relative to Euro-American *Mycobacterium tuberculosis*: An Update. *FEMS Immunol. Med. Microbiol.* **2010**, *58*, 102–105. [CrossRef]
175. Palisson, A.; Courcoul, A.; Durand, B. Role of Cattle Movements in Bovine Tuberculosis Spread in France between 2005 and 2014. *PLoS ONE* **2016**, *11*, e0152578. [CrossRef]
176. Pereira, A.C.; Reis, A.C.; Ramos, B.; Cunha, M.V. Animal Tuberculosis: Impact of Disease Heterogeneity in Transmission, Diagnosis and Control. *Transbound. Emerg. Dis.* **2020**, *2019*, 13539. [CrossRef]
177. Jones, B.A.; Grace, D.; Kock, R.; Alonso, S.; Rushton, J.; Said, M.Y.; McKeever, D.; Mutua, F.; Young, J.; McDermott, J.; et al. Zoonosis Emergence Linked to Agricultural Intensification and Environmental Change. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 8399–8404. [CrossRef] [PubMed]
178. Gopal, R.; Goodchild, A.; Hewinson, G.; de la Rua Domenech, R.; Clifton-Hadley, R. Introduction of Bovine Tuberculosis to North-East England by Bought-in Cattle. *Vet. Rec.* **2006**, *159*, 265–271. [CrossRef] [PubMed]
179. Brooks-Pollock, E.; Roberts, G.O.; Keeling, M.J. A Dynamic Model of Bovine Tuberculosis Spread and Control in Great Britain. *Nature* **2014**, *511*, 228–231. [CrossRef]
180. Reynolds, D. A Review of Tuberculosis Science and Policy in Great Britain. *Vet. Microbiol.* **2006**, *112*, 119–126. [CrossRef] [PubMed]
181. Mosavari, N.; Feizabadi, M.M.; Jamshidian, M.; Shahpouri, M.R.S.; Forbes, K.J.; Pajoohi, R.A.; Keshavarz, R.; Taheri, M.M.; Tadayon, K. Molecular Genotyping and Epidemiology of *Mycobacterium bovis* Strains Obtained from Cattle in Iran. *Vet. Microbiol.* **2011**, *151*, 148–152. [CrossRef]
182. Pozo, P.; VanderWaal, K.; Grau, A.; de la Cruz, M.L.; Nacar, J.; Bezos, J.; Perez, A.; Minguez, O.; Alvarez, J. Analysis of the Cattle Movement Network and Its Association with the Risk of Bovine Tuberculosis at the Farm Level in Castilla y Leon, Spain. *Transbound. Emerg. Dis.* **2019**, *66*, 327–340. [CrossRef]
183. Sylvester, T.T.; Martin, L.E.R.; Buss, P.; Loxton, A.G.; Hausler, G.A.; Rossouw, L.; van Helden, P.; Parsons, S.D.C.; Olea-Popelka, F.; Miller, M.A. Prevalence and Risk Factors for *Mycobacterium bovis* Infection in African Lions (*Panthera leo*) in the Kruger National Park. *J. Wildl. Dis.* **2017**, *53*, 372–376. [CrossRef]
184. Botha, L.; Gey van Pittius, N.C.; van Helden, P.D. Mycobacteria and Disease in Southern Africa. *Transbound. Emerg. Dis.* **2013**, *60* (Suppl. S1), 147–156. [CrossRef]
185. Corner, L.A.L.; Murphy, D.; Gormley, E. *Mycobacterium bovis* Infection in the Eurasian Badger (*Meles meles*): The Disease, Pathogenesis, Epidemiology and Control. *J. Comp. Pathol.* **2011**, *144*, 1–24. [CrossRef]
186. Corner, L.A.L.; O'Meara, D.; Costello, E.; Lesellier, S.; Gormley, E. The Distribution of *Mycobacterium bovis* Infection in Naturally Infected Badgers. *Vet. J.* **2012**, *194*, 166–172. [CrossRef]
187. Turgenbayev, K.A.; Borsynbayeva, A.M.; Plazun, A.A.; Turgenbayev, R.K. Tuberculosis Prevalence in Animals and Humans in the Republic of Kazakhstan. *Vet. World* **2021**, *14*, 2362–2370. [CrossRef] [PubMed]
188. Luciano, S.A.; Roess, A. Human Zoonotic Tuberculosis and Livestock Exposure in Low- and Middle-Income Countries: A Systematic Review Identifying Challenges in Laboratory Diagnosis. *Zoonoses Public Health* **2020**, *67*, 97–111. [CrossRef]
189. Sichewo, P.R.; Etter, E.M.C.C.; Michel, A.L. Wildlife-Cattle Interactions Emerge as Drivers of Bovine Tuberculosis in Traditionally Farmed Cattle. *Prev. Vet. Med.* **2020**, *174*, 104847. [CrossRef]
190. Sichewo, P.R.; Hlokwe, T.M.; Etter, E.M.C.C.; Michel, A.L. Tracing Cross Species Transmission of *Mycobacterium bovis* at the Wildlife / Livestock Interface in South Africa. *BMC Microbiol.* **2020**, *20*, 49. [CrossRef]
191. Etter, E.; Donado, P.; Jori, F.; Caron, A.; Goutard, F.; Roger, F. Risk Analysis and Bovine Tuberculosis, a Re-Emerging Zoonosis. *Ann. N. Y. Acad. Sci.* **2006**, *1081*, 61–73. [CrossRef]
192. Thoen, C.; LoBue, P.; De Kantor, I. The Importance of *Mycobacterium bovis* as a Zoonosis. *Vet. Microbiol.* **2006**, *112*, 339–345. [CrossRef]
193. Awah Ndukum, J.; Caleb Kudi, A.; Bradley, G.; Ane-Anyangwe, I.N.; Fon-Tebug, S.; Tchoumboue, J. Prevalence of Bovine Tuberculosis in Abattoirs of the Littoral and Western Highland Regions of Cameroon: A Cause for Public Health Concern. *Vet. Med. Int.* **2010**, *2010*, 495015. [CrossRef]
194. Ali, Z.I.; Hanafy, M.; Hansen, C.; Saudi, A.M.; Talaat, A.M. Genotypic Analysis of Nontuberculous Mycobacteria Isolated from Raw Milk and Human Cases in Wisconsin. *J. Dairy Sci.* **2020**, *104*, 211–220. [CrossRef]
195. Collins, Á.B.; Floyd, S.; Gordon, S.V.; More, S.J. Prevalence of *Mycobacterium bovis* in Milk on Dairy Cattle Farms: An International Systematic Literature Review and Meta-Analysis. *Tuberculosis* **2022**, *132*, 102166. [CrossRef] [PubMed]

196. Bapat, P.R.; Dodkey, R.S.; Shekhawat, S.D.; Husain, A.A.; Nayak, A.R.; Kawle, A.P.; Daginawala, H.F.; Singh, L.K.; Kashyap, R.S. Prevalence of Zoonotic Tuberculosis and Associated Risk Factors in Central Indian Populations. *J. Epidemiol. Glob. Health* **2017**, *7*, 277–283. [CrossRef] [PubMed]
197. Desta, G.B.; Jena, P.K.; Hassen, H.M.; Behera, M.R. Factors Associated with Zoonosis and Reverse Zoonosis of *Mycobacterium tuberculosis* and *Mycobacterium bovis* in Ethiopia: A Systematic Review and Meta-Analysis. *Int. J. Health Sci.* **2022**, *6*, 1630–1653. [CrossRef]
198. Tober, A.V.; Govender, D.; Russo, I.-R.M.; Cable, J. The Microscopic Five of the Big Five: Managing Zoonotic Diseases within and beyond African Wildlife Protected Areas. *Adv. Parasitol.* **2022**, *117*, 1–46. [CrossRef] [PubMed]
199. Dürr, S.; Müller, B.; Alonso, S.; Hattendorf, J.; Laisse, C.J.M.; van Helden, P.D.; Zinsstag, J. Differences in Primary Sites of Infection between Zoonotic and Human Tuberculosis: Results from a Worldwide Systematic Review. *PLoS Negl. Trop. Dis.* **2013**, *7*, e2399. [CrossRef] [PubMed]
200. Thoen, C.O.; LoBue, P.A.; Enarson, D.A. Tuberculosis in Animals and Humans: An Overview. *Int. J. Tuberc. Lung Dis.* **2010**, *14*, 1075–1078. [CrossRef]
201. Carruth, L.; Roess, A.A.; Mekonnen, Y.T.; Melaku, S.K.; Nichter, M.; Salman, M. Zoonotic Tuberculosis in Africa: Challenges and Ways Forward. *Lancet* **2016**, *388*, 2460–2461. [CrossRef]
202. Kock, R.; Michel, A.L.; Yeboah-Manu, D.; Azhar, E.I.; Torrelles, J.B.; Cadmus, S.I.; Brunton, L.; Chakaya, J.M.; Marais, B.; Mboera, L.; et al. Zoonotic Tuberculosis–The Changing Landscape. *Int. J. Infect. Dis.* **2021**, *113*, S68–S72. [CrossRef]
203. van den Brom, R.; de Jong, A.; van Engelen, E.; Heuvelink, A.; Vellema, P. Zoonotic Risks of Pathogens from Sheep and Their Milk Borne Transmission. *Small Rumin. Res.* **2020**, *189*, 106123. [CrossRef]
204. Drain, P.K.; Bajema, K.L.; Dowdy, D.; Dheda, K.; Naidoo, K.; Schumacher, S.G.; Ma, S.; Meermeier, E.; Lewinsohn, D.M.; Sherman, D.R.; et al. Incipient and Subclinical Tuberculosis: A Clinical Review of Early Stages and Progression of Infection. *Clin. Microbiol. Rev.* **2018**, *31*, e00021-18. [CrossRef]
205. Dutta, N.K.; Karakousis, P.C. Latent Tuberculosis Infection: Myths, Models, and Molecular Mechanisms. *Microbiol. Mol. Biol. Rev.* **2014**, *78*, 343–371. [CrossRef]
206. Furin, J.; Cox, H.; Pai, M. Tuberculosis. *Lancet* **2019**, *393*, 1642–1656. [CrossRef]
207. Esmail, H.; Barry, C.E.; Wilkinson, R.J. Understanding Latent Tuberculosis: The Key to Improved Diagnostic and Novel Treatment Strategies. *Drug Discov. Today* **2012**, *17*, 514–521. [CrossRef] [PubMed]
208. Suárez, I.; Fünger, S.M.; Kröger, S.; Rademacher, J.; Gerd Fätkenheuer, J.; Rybniker, A. The Diagnosis and Treatment of Tuberculosis. *Dtsch. Arztebl. Int.* **2019**, *116*, 729–735. [CrossRef] [PubMed]
209. Zumla, A.I.; Lawn, S.D. Tuberculosis. *Lancet* **2011**, *378*, 57–72. [CrossRef] [PubMed]
210. Faryar, K.A.; Braun, R.; Ancona, R.M.; Ajayi, E.; Bryant, W.; Rehman, S.; Sall, H.; Lyons, M.S.; Huaman, M.A. Emergency Department Screening for Latent Tuberculosis Infection. *Am. J. Emerg. Med.* **2021**, *54*, 323.e5–323.e8. [CrossRef]
211. Houben, R.M.G.J.; Dodd, P.J. The Global Burden of Latent Tuberculosis Infection: A Re-Estimation Using Mathematical Modelling. *PLoS Med.* **2016**, *13*, e1002152. [CrossRef]
212. Bañuls, A.L.; Sanou, A.; Van Anh, N.T.; Godreuil, S. *Mycobacterium tuberculosis*: Ecology and Evolution of a Human Bacterium. *J. Med. Microbiol.* **2015**, *64*, 1261–1269. [CrossRef]
213. Hershberg, R.; Lipatov, M.; Small, P.M.; Sheffer, H.; Niemann, S.; Homolka, S.; Roach, J.C.; Kremer, K.; Petrov, D.A.; Feldman, M.W.; et al. High Functional Diversity in *Mycobacterium tuberculosis* Driven by Genetic Drift and Human Demography. *PLoS Biol.* **2008**, *6*, 2658–2671. [CrossRef]
214. Parbhoo, T.; Sampson, S.L.; Mouton, J.M. Recent Developments in the Application of Flow Cytometry to Advance Our Understanding of *Mycobacterium tuberculosis* Physiology and Pathogenesis. *Cytom. Part A* **2020**, *97*, 683–693. [CrossRef]
215. Gengenbacher, M.; Kaufmann, S.H.E. *Mycobacterium tuberculosis*: Success through Dormancy. *FEMS Microbiol. Rev.* **2012**, *36*, 514–532. [CrossRef]
216. Borah, K.; Xu, Y.; McFadden, J. Dissecting Host-Pathogen Interactions in TB Using Systems-Based Omic Approaches. *Front. Immunol.* **2021**, *12*, 762315. [CrossRef]
217. Gagneux, S.; DeRiemer, K.; Van, T.; Kato-Maeda, M.; De Jong, B.C.; Narayanan, S.; Nicol, M.; Niemann, S.; Kremeri, K.; Gutierrez, M.C.; et al. Variable Host-Pathogen Compatibility in *Mycobacterium tuberculosis*. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 2869–2873. [CrossRef]
218. Manina, G.; Dhar, N.; McKinney, J.D. Stress and Host Immunity Amplify *Mycobacterium tuberculosis* Phenotypic Heterogeneity and Induce Nongrowing Metabolically Active Forms. *Cell Host Microbe* **2015**, *17*, 32–46. [CrossRef] [PubMed]
219. Laureillard, D.; Marcy, O.; Madec, Y.; Chea, S.; Chan, S.; Borand, L.; Fernandez, M.; Prak, N.; Kim, C.; Dim, B.; et al. Paradoxical Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome after Early Initiation of Antiretroviral Therapy in a Randomized Clinical Trial. *Aids* **2013**, *27*, 2577–2586. [CrossRef] [PubMed]
220. Varela-Castro, L.; Barral, M.; Arnal, M.C.; Luco, D.F.D.; Gortázar, C.; Garrido, J.M.; Sevilla, I.A. Beyond Tuberculosis: Diversity and Implications of Non-Tuberculous Mycobacteria at the Wildlife-Livestock Interface. *Transbound. Emerg. Dis.* **2022**. [CrossRef]
221. Keet, D.F.; Michel, A.L.; Bengis, R.G.; Becker, P.; van Dyk, D.S.; van Vuuren, M.; Rutten, V.P.M.G.; Penzhorn, B.L. Intradermal Tuberculin Testing of Wild African Lions (*Panthera leo*) Naturally Exposed to Infection with *Mycobacterium bovis*. *Vet. Microbiol.* **2010**, *144*, 384–391. [CrossRef] [PubMed]

222. Riska, P.F.; Carleton, S. Latent Tuberculosis: Models, Mechanisms, and Novel Prospects for Eradication. *Semin. Pediatr. Infect. Dis.* **2002**, *13*, 263–272. [CrossRef]
223. Meier, N.R.; Jacobsen, M.; Ottenhoff, T.H.M.; Ritz, N. A Systematic Review on Novel *Mycobacterium tuberculosis* Antigens and Their Discriminatory Potential for the Diagnosis of Latent and Active Tuberculosis. *Front. Immunol.* **2018**, *9*, 2476. [CrossRef]
224. Helaine, S.; AM, C.; KG, W.; LM, F.; SA, M.; DW, H.; Helaine, S.; Cheverton, A.M.; Watson, K.G.; Faure, L.M.; et al. Internalization of Salmonella by Macrophages Induces Formation of Nonreplicating Persisters. *Science* **2014**, *343*, 204–208. [CrossRef] [PubMed]
225. Mouton, J.M.; Helaine, S.; Holden, D.W.; Sampson, S.L. Elucidating Population-Wide Mycobacterial Replication Dynamics at the Single-Cell Level. *Microbiology* **2016**, *162*, 966–978. [CrossRef]
226. Chengalroyen, M.D.; Beukes, G.M.; Gordhan, B.G.; Streicher, E.M.; Churchyard, G.; Hafner, R.; Warren, R.; Otwombe, K.; Martinson, N.; Kana, B.D. Detection and Quantification of Differentially Culturable Tubercle Bacteria in Sputum from Patients with Tuberculosis. *Am. J. Respir. Crit. Care Med.* **2016**, *194*, 1532–1540. [CrossRef]
227. Chao, M.C.; Rubin, E.J. Letting Sleeping *Dos* Lie: Does Dormancy Play a Role in Tuberculosis? *Annu. Rev. Microbiol.* **2010**, *64*, 293–311. [CrossRef]
228. Hice, S.A.; Santoscoy, M.C.; Soupir, M.L.; Cademartiri, R. Distinguishing between Metabolically Active and Dormant Bacteria on Paper. *Appl. Microbiol. Biotechnol.* **2018**, *102*, 367–375. [CrossRef] [PubMed]
229. Zhang, Y. Persisters, Persistent Infections and the Yin-Yang Model. *Emerg. Microbes Infect.* **2014**, *3*, 1–10. [CrossRef] [PubMed]
230. Brauner, A.; Fridman, O.; Gefen, O.; Balaban, N.Q. Distinguishing between Resistance, Tolerance and Persistence to Antibiotic Treatment. *Nat. Rev. Microbiol.* **2016**, *14*, 320–330. [CrossRef] [PubMed]
231. Balaban, N.Q.; Gerdes, K.; Lewis, K.; McKinney, J.D. A Problem of Persistence: Still More Questions than Answers? *Nat. Rev. Microbiol.* **2013**, *11*, 587–591. [CrossRef] [PubMed]
232. Balaban, N.Q.; Merrin, J.; Chait, R.; Kowalik, L.; Leibler, S. Bacterial Persistence as a Phenotypic Switch. *Science* **2004**, *305*, 1622–1625. [CrossRef]
233. Li, L.; Mendis, N.; Trigui, H.; Oliver, J.D.; Sebastien, P. The Importance of the Viable but Non-Culturable State in Human Bacterial Pathogens. *Front. Microbiol.* **2014**, *5*, 258. [CrossRef]
234. Buddle, B.M.; Vordermeier, H.M.; Hewinson, R.G. Experimental Infection Models of Tuberculosis in Domestic Livestock. *Microbiol. Spectr.* **2016**, *4*, 4. [CrossRef]
235. Domingo, M.; Vidal, E.; Marco, A. Pathology of Bovine Tuberculosis. *Res. Vet. Sci.* **2014**, *97*, S20–S29. [CrossRef]
236. Thoen, C.O. Tuberculosis in Wild and Domestic Mammals. *Tuberculosis* **1994**, 157–162. [CrossRef]
237. Courtenay, O.; Reilly, L.A.; Sweeney, F.P.; Hibberd, V.; Bryan, S.; Ul-Hassan, A.; Newman, C.; Macdonald, D.W.; Delahay, R.J.; Wilson, G.J.; et al. Is *Mycobacterium bovis* in the Environment Important for the Persistence of Bovine Tuberculosis? *Biol. Lett.* **2006**, *2*, 460–462. [CrossRef] [PubMed]
238. Ghodbane, R.; Medie, F.M.; Lepidi, H.; Nappez, C.; Drancourt, M. Long-Term Survival of Tuberculosis Complex Mycobacteria in Soil. *Microbiology* **2014**, *160 Pt 3*, 496–501. [CrossRef] [PubMed]
239. Lyashchenko, K.P.; Sikar-Gang, A.; Sridhara, A.A.; Johnathan-Lee, A.; Elahi, R.; Lambotte, P.; Esfandiari, J.; Duthi, M.; Reed, S.G.; Jones, G.; et al. Novel Polyprotein Antigens Designed for Improved Serodiagnosis of Bovine Tuberculosis. *Vet. Immunol. Immunopathol.* **2021**, *240*, 110320. [CrossRef]
240. Lyashchenko, K.P.; Gortázar, C.; Miller, M.A.; Waters, W.R. Spectrum of Antibody Profiles in Tuberculous Elephants, Cervids, and Cattle. *Vet. Microbiol.* **2018**, *214*, 89–92. [CrossRef] [PubMed]
241. Thomas, R.; Chambers, M. Review of Methods Used for Diagnosing Tuberculosis in Captive and Free-Ranging Non-Bovid Species (2012–2020). *Pathogens* **2021**, *10*, 584. [CrossRef] [PubMed]
242. Boadella, M.; Lyashchenko, K.; Greenwald, R.; Esfandiari, J.; Jaroso, R.; Carta, T.; Garrido, J.M.; Vicente, J.; de la Fuente, J.; Gortázar, C. Serologic Tests for Detecting Antibodies against *Mycobacterium bovis* and *Mycobacterium avium* Subspecies Paratuberculosis in Eurasian Wild Boar (*Sus scrofa scrofa*). *J. Vet. Diagn. Investig.* **2011**, *23*, 77–83. [CrossRef] [PubMed]
243. Higgitt, R.L.; Buss, P.E.; Van Helden, P.D.; Miller, M.A.; Parsons, S.D.C. Development of Gene Expression Assays Measuring Immune Responses in the Spotted Hyena (*Crocuta crocuta*). *Afr. Zool.* **2017**, *52*, 99–104. [CrossRef]
244. Whelan, A.O.; Coad, M.; Cockle, P.J.; Hewinson, G.; Vordermeier, M.; Gordon, S.V. Revisiting Host Preference in the *Mycobacterium tuberculosis* Complex: Experimental Infection Shows *Mycobacterium tuberculosis* H37Rv to Be Avirulent in Cattle. *PLoS ONE* **2010**, *5*, e8527. [CrossRef]
245. Parikka, M.; Hammarén, M.M.; Harjula, S.-K.E.; Halfpenny, N.J.A.; Oksanen, K.E.; Lahtinen, M.J.; Pajula, E.T.; Iivanainen, A.; Pesu, M.; Rämet, M. *Mycobacterium marinum* Causes a Latent Infection That Can Be Reactivated by Gamma Irradiation in Adult Zebrafish. *PLoS Pathog.* **2012**, *8*, e1002944. [CrossRef]
246. Ramos, D.F.; Silva, P.E.A.; Dellagostin, O.A. Diagnosis of Bovine Tuberculosis: Review of Main Techniques. *Braz. J. Biol.* **2015**, *75*, 830–837. [CrossRef]
247. Warren, R.M.; Gey Van Pittius, N.C.; Barnard, M.; Hesseling, A.; Engelke, E.; De Kock, M.; Gutierrez, M.C.; Chege, G.K.; Victor, T.C.; Hoal, E.G.; et al. Differentiation of *Mycobacterium tuberculosis* Complex by PCR Amplification of Genomic Regions of Difference. *Int. J. Tuberc. Lung Dis.* **2006**, *10*, 818–822.
248. Gong, W.; Wu, X. Differential Diagnosis of Latent Tuberculosis Infection and Active Tuberculosis: A Key to a Successful Tuberculosis Control Strategy. *Front. Microbiol.* **2021**, *12*, 745592. [CrossRef]

249. Bigi, F.; Zumárraga, J.; Cataldi, A.A.; Soria, M.A. Polymorphisms of Twenty Regulatory Proteins between *Mycobacterium tuberculosis* and *Mycobacterium bovis*. *Microbiol. Immunol.* **2016**, *60*, 552–560. [CrossRef]
250. Li, P.; Wang, R.; Dong, W.; Hu, L.; Zong, B.; Zhang, Y.; Wang, X.; Guo, A.; Zhang, A.; Xiang, Y.; et al. Comparative Proteomics Analysis of Human Macrophages Infected with Virulent *Mycobacterium bovis*. *Front. Cell. Infect. Microbiol.* **2017**, *7*, 65. [CrossRef] [PubMed]
251. Meiring, C.; Van Helden, P.; Goosen, W.J. TB Control in Humans and Animals in South Africa: A Perspective on Problems and Successes. *Front. Vet. Sci.* **2018**, *5*, 298. [CrossRef] [PubMed]
252. Lim, A.; Steibel, J.P.; Coussens, P.M.; Grooms, D.L.; Bolin, S.R. Differential Gene Expression Segregates Cattle Confirmed Positive for Bovine Tuberculosis from Antemortem Tuberculosis Test-False Positive Cattle Originating from Herds Free of Bovine Tuberculosis. *Vet. Med. Int.* **2012**, *2012*, 192926. [CrossRef] [PubMed]
253. Patrick, B. Michigan Bovine Tuberculosis Eradication Project: Activities Report. 2003. Available online: https://digitalcommons.unl.edu/michbovinetb/12/ (accessed on 8 March 2022).
254. Parsons, S.D.C.; Cooper, D.; Mccall, A.J.; Mccall, W.A.; Streicher, E.M.; Le Maitre, N.C.; Müller, A.; Gey Van Pittius, N.C.; Warren, R.M.; Van Helden, P.D. Modification of the QuantiFERON-TB Gold (In-Tube) Assay for the Diagnosis of *Mycobacterium bovis* Infection in African buffaloes (*Syncerus caffer*). *Vet. Immunol. Immunopathol.* **2011**, *142*, 113–118. [CrossRef] [PubMed]
255. Pai, M.; Denkinger, C.M.; Kik, S.V.; Rangaka, M.X.; Zwerling, A.; Oxlade, O.; Metcalfe, J.Z.; Cattamanchi, A.; Dowdy, D.W.; Dheda, K.; et al. Gamma Interferon Release Assays for Detection of *Mycobacterium tuberculosis* Infection. *Clin. Microbiol. Rev.* **2014**, *27*, 3–20. [CrossRef]
256. Denis, M.; Wedlock, D.N.; McCarthy, A.R.; Parlane, N.A.; Cockle, P.J.; Vordermeier, H.M.; Hewinson, R.G.; Buddle, B.M. Enhancement of the Sensitivity of the Whole-Blood Gamma Interferon Assay for Diagnosis of *Mycobacterium bovis* Infections in Cattle. *Clin. Vaccine Immunol.* **2007**, *14*, 1483–1489. [CrossRef]
257. Clegg, T.A.; Good, M.; Doyle, M.; Duignan, A.; More, S.J.; Gormley, E. The Performance of the Interferon Gamma Assay When Used as a Diagnostic or Quality Assurance Test in *Mycobacterium bovis* Infected Herds. *Prev. Vet. Med.* **2017**, *140*, 116–121. [CrossRef]
258. Frederico, O.; Id, I.; Soares, P.; Yumi, C.; Id, I.; Machado, A.; Ferreira, S.; Id, N.; Id, B.H.; Acha, S.J.; et al. Evolutionary Analysis of *Mycobacterium bovis* Genotypes across Africa Suggests Co-Evolution with Livestock and Humans. *PLoS Negl. Trop. Dis.* **2020**, *14*, e0008081. [CrossRef]
259. Sukumar, R.; Joshi, B.; Lagrange, P.H.; Ophe Longuet, C.; Verma-Kumar, S.; Abraham, D.; Dendukuri, N.; Cheeran, J.V.; Narayanaswamy Balaji, K. Serodiagnosis of Tuberculosis in Asian Elephants (*Elephas maximus*) in Southern India: A Latent Class Analysis. *PLoS ONE* **2012**, *7*, e49548. [CrossRef]
260. Golby, P.; Hatch, K.A.; Bacon, J.; Cooney, R.; Riley, P.; Allnutt, J.; Hinds, J.; Nunez, J.; Marsh, P.D.; Hewinson, R.G.; et al. Comparative Transcriptomics Reveals Key Gene Expression Differences between the Human and Bovine Pathogens of the *Mycobacterium tuberculosis* Complex. *Microbiology* **2007**, *153*, 3323–3336. [CrossRef] [PubMed]
261. Garnier, T.; Eiglmeier, K.; Camus, J.C.; Medina, N.; Mansoor, H.; Pryor, M.; Duthoy, S.; Grondin, S.; Lacroix, C.; Monsempe, C.; et al. The Complete Genome Sequence of *Mycobacterium bovis*. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 7877–7882. [CrossRef]
262. Marimani, M.; Ahmad, A.; Duse, A. The Role of Epigenetics, Bacterial and Host Factors in Progression of *Mycobacterium tuberculosis* Infection. *Tuberculosis* **2018**, *113*, 200–214. [CrossRef]
263. Keating, L.A.; Wheeler, P.R.; Mansoor, H.; Inwald, J.K.; Dale, J.; Hewinson, R.G.; Gordon, S.V. The Pyruvate Requirement of Some Members of the *Mycobacterium tuberculosis* Complex Is Due to an Inactive Pyruvate Kinase: Implications for in vivo Growth. *Mol. Microbiol.* **2005**, *56*, 163–174. [CrossRef]
264. Sohaskey, C.D.; Modesti, L. Differences in Nitrate Reduction between *Mycobacterium tuberculosis* and *Mycobacterium bovis* Are Due to Differential Expression of Both NarGHJI and NarK2. *FEMS Microbiol. Lett.* **2009**, *290*, 129–134. [CrossRef]
265. Queval, C.J.; Fearns, A.; Botella, L.; Smyth, A.; Schnettger, L.; Mitermite, M.; Wooff, E.; Villarreal-Ramos, B.; Garcia-Jimenezi, W.; Heunis, T.; et al. Macrophage-Specific Responses to Humanand Animal-Adapted Tubercle Bacilli Reveal Pathogen and Host Factors Driving Multinucleated Cell Formation. *PLoS Pathog.* **2021**, *17*, e1009410. [CrossRef]
266. Cheng, G.; Hussain, T.; Sabir, N.; Ni, J.; Li, M.; Zhao, D.; Zhou, X. Comparative Study of the Molecular Basis of Pathogenicity of *Mycobacterium bovis* Strains in a Mouse Model. *Int. J. Mol. Sci.* **2019**, *20*, 5. [CrossRef]
267. Nedeltchev, G.G.; Raghunand, T.R.; Jassal, M.S.; Lun, S.; Cheng, Q.J.; Bishai, W.R. Extrapulmonary Dissemination of *Mycobacterium bovis* but Not *Mycobacterium tuberculosis* in a Bronchoscopic Rabbit Model of Cavitary Tuberculosis. *Infect. Immun.* **2009**, *77*, 598–603. [CrossRef]
268. Palmer, M.V.; Thacker, T.C.; Kanipe, C.; Boggiatto, P.M.; Palmer, M.V. Heterogeneity of Pulmonary Granulomas in Cattle Experimentally Infected with *Mycobacterium bovis*. *Front. Vet. Sci.* **2021**, *8*, 671460. [CrossRef] [PubMed]
269. Mouton, J.M.; Heunis, T.; Dippenaar, A.; Gallant, J.L.; Kleynhans, L.; Sampson, S.L. Comprehensive Characterization of the Attenuated Double Auxotroph *Mycobacterium tuberculosis*Δ*leud*Δ*panCD* as an Alternative to H37Rv. *Front. Microbiol.* **2019**, *10*, 1922. [CrossRef] [PubMed]
270. Voskuil, M.I.; Schnappinger, D.; Visconti, K.C.; Harrell, M.I.; Dolganov, G.M.; Sherman, D.R.; Schoolnik, G.K. Inhibition of Respiration by Nitric Oxide Induces a *Mycobacterium tuberculosis* Dormancy Program. *J. Exp. Med.* **2003**, *198*, 705–713. [CrossRef]
271. Tullius, M.V.; Harth, G.; Horwitz, M.A. Glutamine Synthetase GlnA1 Is Essential for Growth of *Mycobacterium tuberculosis* in Human THP-1 Macrophages and Guinea Pigs. *Infect. Immun.* **2003**, *71*, 3927–3936. [CrossRef]

272. Nozaki, Y.; Hasegawa, Y.; Ichiyama, S.; Nakashima, I.; Shimokata, K. Mechanism of Nitric Oxide-Dependent Killing of *Mycobacterium bovis* BCG in Human Alveolar Macrophages. *Infect. Immun.* **1997**, *65*, 3644–3647. [CrossRef] [PubMed]
273. Denis, M. Interferon-Gamma-Treated Murine Macrophages Inhibit Growth of Tubercle Bacilli via the Generation of Reactive Nitrogen Intermediates. *Cell. Immunol.* **1991**, *132*, 150–157. [CrossRef]
274. Hutter, B.; Dick, T. Up-Regulation of NarX, Encoding a Putative "fused Nitrate Reductase" in Anaerobic Dormant *Mycobacterium bovis* BCG. *FEMS Microbiol. Lett.* **1999**, *178*, 63–69. [CrossRef] [PubMed]
275. Boon, C.; Dick, T. *Mycobacterium bovis* BCG Response Regulator Essential for Hypoxic Dormancy. *J. Bacteriol.* **2002**, *184*, 6760–6767. [CrossRef]
276. Slavchev, G.; Michailova, L.; Markova, N. Stress-Induced L-Forms of *Mycobacterium bovis*: A Challenge to Survivability. *New Microbiol.* **2013**, *36*, 157–166.
277. Rodriguez, J.G.; Burbano, C.S.; Nuñez, C.; González, C.E.; Zambrano, M.M.; García, M.J.; Del Portillo, P. Rv3134c/DevR/DevS Operon of *Mycobacterium bovis* BCG Is Differentially Transcribed under "in vitro" Stress Conditions. *Tuberculosis* **2008**, *88*, 273–282. [CrossRef]
278. Malherbe, S.T.; Shenai, S.; Ronacher, K.; Loxton, A.G.; Dolganov, G.; Kriel, M.; Van, T.; Chen, R.Y.; Warwick, J.; Via, E.; et al. Persisting PET-CT Lesion Activity and *Mycobacterium tuberculosis* mRNA after Pulmonary Tuberculosis Cure. *Nat. Med.* **2016**, *22*, 1094–1100. [CrossRef] [PubMed]
279. Scanga, C.A.; Mohan, V.P.; Joseph, H.; Yu, K.; Chan, J.; Flynn, J.L. Reactivation of Latent Tuberculosis: Variations on the Cornell Murine Model. *Infect. Immun.* **1999**, *67*, 4531–4538. [CrossRef] [PubMed]
280. Palacios, J.J.; Navarro, Y.; Romero, B.; Penedo, A.; Menéndez González, Á.; Pérez Hernández, M.D.; Fernández-Verdugo, A.; Copano, F.; Torreblanca, A.; Bouza, E.; et al. Molecular and Epidemiological Population-Based Integrative Analysis of Human and Animal *Mycobacterium bovis* Infections in a Low-Prevalence Setting. *Vet. Microbiol.* **2016**, *195*, 30–36. [CrossRef]
281. Larsen, M.V.; Sørensen, I.J.; Thomsen, V.; Ravn, P. Re-Activation of Bovine Tuberculosis in a Patient Treated with Infliximab. *Eur. Respir. J.* **2008**, *32*, 229–231. [CrossRef]
282. Cosivi, O.; Grange, J.M.; Daborn, C.J.; Raviglione, M.C.; Fujikura, T.; Cousins, D.; Robinson, R.A.; Huchzermeyer, H.F.A.K.; De Kantor, I.; Meslin, F.X. Zoonotic Tuberculosis Due to *Mycobacterium bovis* in Developing Countries. *Emerg. Infect. Dis.* **1998**, *4*, 59–70. [CrossRef]
283. Shahmohammadi, S.; Saffar, M.J.; Rezai, M.S. BCG-Osis after BCG Vaccination in Immunocompromised Children: Case Series and Review. *J. Pediatr. Rev.* **2014**, *2*, 62–74. [CrossRef]
284. Bhola, R.K.; Sarangi, R.; Dey, P.; Samal, P. Disseminated BCG-Osis with Haemophagocytosis, Tubercular Bacteraemia, and Unusual Haematological Findings with Its Haematology Analyser-Based Expression. *J. Hematop.* **2018**, *11*, 87–92. [CrossRef]
285. Gibson, S.E.R.; Harrison, J.; Cox, J.A.G. Modelling a Silent Epidemic: A Review of the in vitro Models of Latent Tuberculosis. *Pathogens* **2018**, *7*, 88. [CrossRef]
286. Alnimr, A.M. Dormancy Models for *Mycobacterium tuberculosis*: A Minireview. *Brazilian J. Microbiol.* **2015**, *46*, 641–647. [CrossRef]
287. Kundu, M.; Basu, J. Applications of Transcriptomics and Proteomics for Understanding Dormancy and Resuscitation in *Mycobacterium tuberculosis*. *Front. Microbiol.* **2021**, *12*, 642487. [CrossRef]
288. Gideon, H.P.; Wilkinson, K.A.; Rustad, T.R.; Oni, T.; Guio, H.; Kozak, R.A.; Sherman, D.R.; Meintjes, G.; Behr, M.A.; Vordermeier, H.M.; et al. Hypoxia Induces an Immunodominant Target of Tuberculosis Specific T Cells Absent from Common BCG Vaccines. *PLoS Pathog.* **2010**, *6*, e1001237. [CrossRef]
289. Deb, C.; Lee, C.M.; Dubey, V.S.; Daniel, J.; Abomoelak, B.; Sirakova, T.D.; Pawar, S.; Rogers, L.; Kolattukudy, P.E. A Novel in vitro Multiple-Stress Dormancy Model for *Mycobacterium tuberculosis* Generates a Lipid-Loaded, Drug-Tolerant, Dormant Pathogen. *PLoS ONE* **2009**, *4*, e6077. [CrossRef] [PubMed]
290. Rao, M.; Streur, T.L.; Aldwell, F.E.; Cook, G.M. Intracellular PH Regulation by *Mycobacterium smegmatis* and *Mycobacterium bovis* BCG. *Microbiology.* **2001**, *147*, 1017–1024. [CrossRef] [PubMed]
291. Gallant, J.L.; Viljoen, A.J.; Van Helden, P.D.; Wiid, I.J.F. Glutamate Dehydrogenase Is Required by *Mycobacterium bovis* BCG for Resistance to Cellular Stress. *PLoS ONE* **2016**, *11*, 147706. [CrossRef] [PubMed]
292. Weiss, D.J.; Evanson, O.A.; Moritz, A.; Deng, M.Q.; Abrahamsen, M.S. Differential Responses of Bovine Macrophages to *Mycobacterium avium* Subsp. paratuberculosis and Mycobacterium avium Subsp. avium. *Infect. Immun.* **2002**, *70*, 5556–5561. [CrossRef] [PubMed]
293. Piercy, J.; Werling, D.; Coffey, T.J. Differential Responses of Bovine Macrophages to Infection with Bovine-Specific and Non-Bovine Specific Mycobacteria. *Tuberculosis* **2007**, *87*, 415–420. [CrossRef]
294. Medley, J.; Goff, A.; Bettencourt, P.J.G.; Dare, M.; Cole, L.; Cantillon, D.; Waddell, S.J. Dissecting the *Mycobacterium bovis* BCG Response to Macrophage Infection to Help Prioritize Targets for Anti-Tuberculosis Drug and Vaccine Discovery. *Vaccines* **2022**, *10*, 113. [CrossRef]
295. Zhan, X.; Yuan, W.; Zhou, Y.; Ma, R.; Ge, Z. Small RNA Sequencing and Bioinformatics Analysis of RAW264.7-Derived Exosomes after *Mycobacterium bovis* Bacillus Calmette-Guérin Infection. *BMC Genom.* **2022**, *23*, 355. [CrossRef]
296. Lin, W.; Xin, T. The Influence of Gene Rv3671c in *Mycobacterium bovis* to Its Replication and Acid Resistance. *bioRxiv* **2020**. [CrossRef]
297. Ma, R.; Farrell, D.; Gonzalez, G.; Browne, J.A.; Nakajima, C.; Suzuki, Y.; Gordon, S.V. The TbD1 Locus Mediates a Hypoxia-Induced Copper Response in *Mycobacterium bovis*. *Front. Microbiol.* **2022**, *13*, 817952. [CrossRef]

298. Malone, K.M.; Rue-Albrecht, K.; Magee, D.A.; Conlon, K.; Schubert, O.T.; Nalpas, N.C.; Browne, J.A.; Smyth, A.; Gormley, E.; Aebersold, R.; et al. Comparative 'omics Analyses Differentiate *Mycobacterium tuberculosis* and *Mycobacterium bovis* and Reveal Distinct Macrophage Responses to Infection with the Human and Bovine Tubercle Bacilli. *Microb. Genom.* **2018**, *4*, 163. [CrossRef] [PubMed]
299. Gibson, A.J.; Passmore, I.J.; Faulkner, V.; Xia, D.; Nobeli, I.; Stiens, J.; Willcocks, S.; Clark, T.G.; Sobkowiak, B.; Werling, D.; et al. Probing Differences in Gene Essentiality Between the Human and Animal Adapted Lineages of the *Mycobacterium tuberculosis* Complex Using TnSeq. *Front. Vet. Sci.* **2021**, *8*, 717. [CrossRef] [PubMed]
300. Jones, G.J.; Pirson, C.; Gideon, H.P.; Wilkinson, K.A.; Sherman, D.R.; Wilkinson, R.J.; Hewinson, R.G.; Vordermeier, H.M. Immune Responses to the Enduring Hypoxic Response Antigen Rv0188 Are Preferentially Detected in *Mycobacterium bovis* Infected Cattle with Low Pathology. *PLoS ONE* **2011**, *6*, e21371. [CrossRef]
301. Larsen, M.H.; Lacourciere, K.; Parker, T.M.; Kraigsley, A.; Achkar, M.; Adams, L.B.; Dupnik, K.M.; Hall-stoodley, L.; Kanipe, C.; Kurtz, S.L.; et al. The Many Hosts of Mycobacteria 8 (MHM8): A Conference Report. *Tuberculosis* **2020**, *8*, 101914. [CrossRef] [PubMed]
302. León, A.D.; Zumárraga, M.J.; Jiménez Oropeza, R.; Gioffré, A.K.; Bernardelli, A.; Orozco Estévez, H.; Cataldi, A.A.; Hernández Pando, R. *Mycobacterium bovis* with Different Genotypes and from Different Hosts Induce Dissimilar Immunopathological Lesions in a Mouse Model of Tuberculosis. *Clin. Exp. Immunol.* **2009**, *157*, 139–147. [CrossRef] [PubMed]
303. Phillips, C.J.C.; Foster, C.R.W.; Morris, P.A.; Teverson, R. The Transmission of *Mycobacterium bovis* Infection to Cattle. *Res. Vet. Sci.* **2003**, *74*, 1–15. [CrossRef]
304. Alvarez Herrera, A. Are Cattle a Surrogate Model for Pathogenic Mycobacterial Latent Infection? *Mycobact. Dis.* **2014**, *4*, 4–5. [CrossRef]
305. Ippolito, D.; Boniotti, M.B.; Fiasconaro, M.; Fontana, S.; Boifava, M.; Ciarello, F.P.; Amato, B.; Pacciarini, M.; Presti, V.D.M.L. Development and Evaluation of a Multi-Antigen Serological Assay for the Intra-Vitam Diagnosis of Tuberculosis Caused by *Mycobacterium bovis* in Pigs. *J. Immunol. Methods* **2022**, *503*, 113234. [CrossRef]
306. Nol, P.; Wehtje, M.E.; Bowen, R.A.; Robbe-austerman, S.; Thacker, T.C.; Lantz, K.; Rhyan, J.C.; Baeten, L.A.; Juste, A.; Sevilla, I.A.; et al. Pathogens E Ff Ects of Inactivated *Mycobacterium bovis* Vaccination on Molokai-Origin Wild Pigs Experimentally Infected with Virulent M. Bovis. *Pathogens* **2020**, *9*, 199. [CrossRef]
307. Bolin, C.A.; Whipple, D.L.; Khanna, K.V.; Risdahl, J.M.; Peterson, P.K.; Molitor, T.W. Infection of Swine with *Mycobacterium bovis* as a Model of Human Tuberculosis. *J. Infect. Dis.* **1997**, *176*, 1559–1566. [CrossRef]
308. Gallagher, J.; Clifton-Hadley, R.S. Tuberculosis in Badgers; a Review of the Disease and Its Significance for Other Animals. *Res. Vet. Sci.* **2000**, *69*, 203–217. [CrossRef] [PubMed]
309. Gallagher, J.; Monies, R.; Gavier-Widen, M.; Rule, B. Role of Infected, Non-Diseased Badgers in the Pathogenesis of Tuberculosis in the Badger. *Vet. Rec.* **1998**, *142*, 710–714. [CrossRef] [PubMed]
310. Kupz, A.; Zedler, U.; Stäber, M.; Kaufmann, S.H.E. A Mouse Model of Latent Tuberculosis Infection to Study Intervention Strategies to Prevent Reactivation. *PLoS ONE* **2016**, *11*, e0158849. [CrossRef] [PubMed]
311. Karakousis, P.C.; Yoshimatsu, T.; Lamichhane, G.; Woolwine, S.C.; Nuermberger, E.L.; Grosset, J.; Bishai, W.R. Dormancy Phenotype Displayed by Extracellular *Mycobacterium tuberculosis* within Artificial Granulomas in Mice. *J. Exp. Med.* **2004**, *200*, 647–657. [CrossRef]
312. Zhan, L.; Tang, J.; Lin, S.; Xu, Y.; Xu, Y.; Qin, C. Prophylactic Use of Ganoderma Lucidum Extract May Inhibit *Mycobacterium tuberculosis* Replication in a New Mouse Model of Spontaneous Latent Tuberculosis Infection. *Front. Microbiol.* **2016**, *6*, 1490. [CrossRef]
313. Rhoades, E.R. Progression of Chronic Pulmonary Tuberculosis in Mice Aerogenically Infected with Virulent *Mycobacterium tuberculosis*. *Tuber. Lung Dis.* **1997**, *78*, 57–66. [CrossRef]
314. Lu, J.B.; Chen, B.W.; Wang, G.Z.; Fu, L.L.; Shen, X.B.; Su, C.; Du, W.X.; Yang, L.; Xu, M. Recombinant Tuberculosis Vaccine AEC/BC02 Induces Antigen-Specific Cellular Responses in Mice and Protects Guinea Pigs in a Model of Latent Infection. *J. Microbiol. Immunol. Infect.* **2015**, *48*, 597–603. [CrossRef]
315. Clark, S.; Hall, Y.; Williams, A. Animal Models of Tuberculosis: Guinea Pigs. *Cold Spring Harb. Perspect. Med.* **2015**, *5*, a018572. [CrossRef]
316. Chambers, M.A.; Williams, A.; Gavier-Widén, D.; Whelan, A.; Hughes, C.; Hall, G.; Lever, M.S.; Marsh, P.D.; Hewinson, R.G. A Guinea Pig Model of Low-Dose *Mycobacterium bovis* Aerogenic Infection. *Vet. Microbiol.* **2001**, *80*, 213–226. [CrossRef]
317. Chandran, A.; Williams, K.; Mendum, T.; Stewart, G.; Clark, S.; Zadi, S.; McLeod, N.; Williams, A.; Villarreal-Ramos, B.; Vordermeier, M.; et al. Development of a Diagnostic Compatible BCG Vaccine against Bovine Tuberculosis. *Sci. Rep.* **2019**, *9*, 17791. [CrossRef]
318. Kashino, S.S.; Napolitano, D.R.; Skobe, Z.; Campos-Neto, A. Guinea Pig Model of *Mycobacterium tuberculosis* Dormant Infection. *Microbes Infect.* **2008**, *10*, 1469–1476. [CrossRef]
319. Lenaerts, A.J.; Chapman, P.L.; Orme, I.M. Statistical Limitations to the Cornell Model of Latent Tuberculosis Infection for the Study of Relapse Rates. *Tuberculosis* **2004**, *84*, 361–364. [CrossRef] [PubMed]
320. Zhan, L.; Tang, J.; Sun, M.; Qin, C. Animal Models for Tuberculosis in Translational and Precision Medicine. *Front. Microbiol.* **2017**, *8*, 717. [CrossRef] [PubMed]

321. Bapat, P.R.; Husain, A.A.; Daginawala, H.F.; Agrawal, N.P.; Panchbhai, M.S.; Satav, A.R.; Taori, G.M.; Kashyap, R.S. The Assessment of Cytokines in Quantiferon Supernatants for the Diagnosis of Latent TB Infection in a Tribal Population of Melghat, India. *J. Infect. Public Health* **2015**, *8*, 329–340. [CrossRef] [PubMed]
322. Sutherland, J.S.; Hill, P.C.; Adetifa, I.M.; de Jong, B.C.; Donkor, S.; Joosten, S.A.; Opmeer, L.; Haks, M.C.; Ottenhoff, T.H.M.; Adegbola, R.A.; et al. Identification of Probable Early-Onset Biomarkers for Tuberculosis Disease Progression. *PLoS ONE* **2011**, *6*, e25230. [CrossRef]
323. Sloot, R.; Schim van der Loeff, M.F.; van Zwet, E.W.; Haks, M.C.; Keizer, S.T.; Scholing, M.; Ottenhoff, T.H.M.; Borgdorff, M.W.; Joosten, S.A. Biomarkers Can Identify Pulmonary Tuberculosis in HIV-Infected Drug Users Months Prior to Clinical Diagnosis. *EbioMedicine* **2015**, *2*, 172–179. [CrossRef]
324. Chegou, N.N.; Black, G.F.; Kidd, M.; van Helden, P.D.; Walzl, G. Host Markers in Quantiferon Supernatants Differentiate Active TB from Latent TB Infection: Preliminary Report. *BMC Pulm. Med.* **2009**, *9*, 21. [CrossRef]
325. Kim, S.Y.; Park, M.S.; Kim, Y.S.; Kim, S.K.; Chang, J.; Lee, H.J.; Cho, S.N.; Kang, Y.A. The Responses of Multiple Cytokines Following Incubation of Whole Blood from TB Patients, Latently Infected Individuals and Controls with the TB Antigens ESAT-6, CFP-10 and TB7.7. *Scand. J. Immunol.* **2012**, *76*, 580–586. [CrossRef]
326. Suzukawa, M.; Akashi, S.; Nagai, H.; Nagase, H.; Nakamura, H.; Matsui, H.; Hebisawa, A.; Ohta, K. Combined Analysis of IFN-γ, IL-2, IL-5, IL-10, IL-1RA and MCP-1 in QFT Supernatant Is Useful for Distinguishing Active Tuberculosis from Latent Infection. *PLoS ONE* **2016**, *11*, e0152483. [CrossRef]
327. Singh, G.; Yadav, M.; Ghosh, C.; Rathore, J.S. Bacterial Toxin-Antitoxin Modules: Classification, Functions, and Association with Persistence. *Curr. Res. Microb. Sci.* **2021**, *2*, 100047. [CrossRef]
328. Boon, C.; Li, R.; Qi, R.; Dick, T. Proteins of *Mycobacterium bovis* BCG Induced in the Wayne Dormancy Model. *J. Bacteriol.* **2001**, *183*, 2672–2676. [CrossRef] [PubMed]
329. Leistikow, R.L.; Morton, R.A.; Bartek, I.L.; Frimpong, I.; Wagner, K.; Voskuil, M.I. The *Mycobacterium tuberculosis* DosR Regulon Assists in Metabolic Homeostasis and Enables Rapid Recovery from Nonrespiring Dormancy. *J. Bacteriol.* **2010**, *192*, 1662–1670. [CrossRef] [PubMed]
330. Arroyo, L.; Marín, D.; Franken, K.L.M.C.; Ottenhoff, T.H.M.; Barrera, L.F. Potential of DosR and Rpf Antigens from *Mycobacterium tuberculosis* to Discriminate between Latent and Active Tuberculosis in a Tuberculosis Endemic Population of Medellin Colombia. *BMC Infect. Dis.* **2018**, *18*, 26. [CrossRef]
331. Black, G.F.; Thiel, B.A.; Ota, M.O.; Parida, S.K.; Adegbola, R.; Boom, W.H.; Dockrell, H.M.; Franken, K.L.M.C.; Friggen, A.H.; Hill, P.C.; et al. Immunogenicity of Novel DosR Regulon-Encoded Candidate Antigens of *Mycobacterium tuberculosis* in Three High-Burden Populations in Africa. *Clin. Vaccine Immunol.* **2009**, *16*, 1203–1212. [CrossRef]
332. Keren, I.; Minami, S.; Rubin, E.; Lewis, K. Characterization and Transcriptome Analysis of *Mycobacterium tuberculosis* Persisters. *mBio* **2011**, *2*, 11. [CrossRef] [PubMed]
333. O' Toole, R.; Smeulders, M.J.; Blokpoel, M.C.; Kay, E.J.; Lougheed, K.; Williams, H.D. A Two-Component Regulator of Universal Stress Protein Expression and Adaptation to Oxygen Starvation in *Mycobacterium smegmatis*. *J. Bacteriol.* **2003**, *185*, 1543–1554. [CrossRef] [PubMed]
334. Stewart, G.R.; Robertson, B.D.; Young, D.B. Tuberculosis: A Problem with Persistence. *Nat. Rev. Microbiol.* **2003**, *1*, 97–105. [CrossRef]
335. Flores-Valdez, M.A.; Aceves-Sánchez, M.D.J.; Peterson, E.J.R.; Baliga, N.; Bravo-Madrigal, J.; De la Cruz-Villegas, M.Á.; Ares, M.A.; Born, S.; Voskuil, M.; Pérez-Padilla, N.A.; et al. Transcriptional Portrait of M. Bovis BCG during Biofilm Production Shows Genes Differentially Expressed during Intercellular Aggregation and Substrate Attachment. *Sci. Rep.* **2020**, *10*, 12578. [CrossRef]
336. Hozumi, H.; Tsujimura, K.; Yamamura, Y.; Seto, S.; Uchijima, M.; Nagata, T.; Miwa, S.; Hayakawa, H.; Fujisawa, T.; Hashimoto, D.; et al. Immunogenicity of Dormancy-Related Antigens in Individuals Infected with *Mycobacterium tuberculosis* in Japan. *Int. J. Tuberc. Lung Dis.* **2013**, *17*, 818–824. [CrossRef]
337. Demaio, J.; Zhang, Y.; Ko, C.; Youngt, D.B.; Bishai, W.R. A Stationary-Phase Stress-Response Sigma Factor from *Mycobacterium tuberculosis*. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 2790–2794. [CrossRef]
338. Michele, T.M.; Ko, C. Exposure to Antibiotics Induces Expression of the *Mycobacterium tuberculosis* SigF Gene: Implications for Chemotherapy against Mycobacterial Persistors. *Society* **2010**, *43*, 218–225. [CrossRef] [PubMed]
339. Williams, E.P.; Lee, J.-H.; Bishai, W.R.; Colantuoni, C.; Karakousis, P.C. *Mycobacterium tuberculosis* SigF Regulates Genes Encoding Cell Wall-Associated Proteins and Directly Regulates the Transcriptional Regulatory Gene PhoY1. *J. Bacteriol.* **2007**, *189*, 4234–4242. [CrossRef] [PubMed]
340. Sherman, R.A.; Shimoda, K.J. Tuberculosis Tracking: Determining the Frequency of the Booster Effect in Patients and Staff. *Am. J. Infect. Control* **2001**, *29*, 7–12. [CrossRef] [PubMed]
341. Jee, B.; Singh, Y.; Yadav, R.; Lang, F. Small Heat Shock Protein16.3 of *Mycobacterium tuberculosis*: After Two Decades of Functional Characterization. *Cell. Physiol. Biochem.* **2018**, *49*, 368–380. [CrossRef]
342. Rodrigue, S.; Provvedi, R.; Jacques, P.É.; Gaudreau, L.; Manganelli, R. The σ Factors of *Mycobacterium tuberculosis*. *FEMS Microbiol. Rev.* **2006**, *30*, 926–941. [CrossRef] [PubMed]
343. Sachdeva, P.; Misra, R.; Tyagi, A.K.; Singh, Y. The Sigma Factors of *Mycobacterium tuberculosis*: Regulation of the Regulators. *FEBS J.* **2010**, *277*, 605–626. [CrossRef]

344. Manganelli, R.; Dubnau, E.; Tyagi, S.; Kramer, F.R.; Smith, I. Differential Expression of 10 Sigma Factor Genes in *Mycobacterium tuberculosis*. *Mol. Microbiol.* **1999**, *30*, 715–724. [CrossRef]
345. Cuerda, M.X.; Colombatti, M.A.; Gravisaco, M.J.; Marfil, M.J.; Barandiaran, S.; Sevilla, I.A.; Garrido, J.M.; Moyano, R.D.; Zumárraga, M.J.; Romano, M.I.; et al. Pathogenesis of Domestic Pigs Submitted to Mycobacterial Sensitizations Previous to Experimental Infection with *Mycobacterium bovis*. *Span. J. Agric. Res.* **2022**, *20*, e0502. [CrossRef]