



Tuberculosis in pigs: a review of the current status

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Abstract. Tuberculosis in animals remains, despite the success of several control plans, a major endemic disease worldwide, and a major infectious zoonosis. Pigs represent the main reservoir for animal tuberculosis in several areas of the world, especially within southern Europe and together with wild ruminants, a major impediment in tuberculosis eradication programs. Recently porcine tuberculosis emerges as an experimental model for animal and human tuberculosis, presenting several advantages compared to some classical *in vivo* TB-models. In this review, we briefly present and discuss the current knowledge on the pathogenesis of tuberculosis in pigs, the reservoir status, the main advantages and disadvantages of swine models of tuberculosis and not least the gross and microscopical features of mycobacteriosis in swine.

Key Words: mycobacterium, porcine, granuloma, reservoir, experimental.

Introduction. Tuberculosis (TB) and other mycobacterial diseases in swine are worldwide diseases and, despite their long history, continues to cause significant economic losses to the porcine industry and husbandry (Arega et al 2013; Pavlas et al 1985). Often overlooked and erroneously neglected as importance (Polaček & Aleksić-Kovačević 2016), pigs are also a reservoir for bovine tuberculosis and occasionally the source of zoonotically-transmitted tuberculosis in humans, especially in TB-endemic areas (Bollo et al 2000; Chambers et al 2018; Nugent et al 2015).

There are no specific *Mycobacterium* species for pigs, they are susceptible to a wide species of mycobacteria, including *Mycobacterium bovis*, *Mycobacterium tuberculosis*, *Mycobacterium africanum*, and *Mycobacterium avium-intracellulare* complex. Other potentially pathogenic species such as *Mycobacterium fortuitum* and *Mycobacterium chelonae*, *Mycobacterium terrae* and *Mycobacterium phlei* (Alfredsen & Saxegaard 1992; Cvetnić et al 2007; Pate et al 2004) can also produce tuberculosis-like of lesions in swine. Occasionally other species of mycobacteria as *M. microti*, *M. chelonae*, *M. terrae*, *M. palustre*, *M. malmoense*, *M. bohemicum*, *M. heckeshornense*, *M. scrofulaceum*-like, *M. gastri*, and *M. fortuitum* are isolated from tuberculosis-like lesions in pigs, but their overall incidence and zoonotic risk are reduced (Brown & Neuman 1979; Dvorská et al 1999; Taylor et al 2006; Thoen and Himes 1977; van Ingen et al 2010). Recently a generalized lymphadenopathy and disseminated granulomas in the lungs, liver, spleen, and kidneys were identified in a pot-bellied pig following infection with *M. kansasii* (Schafbuch et al 2018). It worth to be mentioned that human tuberculosis is produced by bacteria from *Mycobacterium tuberculosis complex* mainly *M. tuberculosis* and occasionally, *M. bovis*, *M. africanum*, *M. caprae*, and *M. canetti*. Some of these species are infecting also the pigs, as described above, raising the question of a possible zoonotic TB transmission (Kiers et al 2008; Richter et al 2003; Thoen et al 2009). Due to the high susceptibility to *M. bovis* infection, pigs are used as screening sentinels for local-environmental presence and load with *M. bovis* (Nugent et al 2002).

The terminology used for designing the diseases produced by *Mycobacterium* species in mammals is "tuberculosis" or "mycobacteriosis". The term "tuberculosis" is

used for diseases caused by *M. tuberculosis* or *M. bovis*, while other conditions that can induce similar lesions are referred to as swine "mycobacteriosis" or porcine "atypical mycobacteriosis" (Maxie 2015). This clear separation as tuberculosis and mycobacteriosis of diseases produced by mycobacteria in pigs is important especially from the perspective of assessment of disease-transmission risk and epidemiology. This clear separation becomes difficult from the gross examination perspective since both groups of diseases produce similar granulomatous lesions located mainly in the lymph nodes draining the head, neck and abdominal-digestive system (Chambers et al 2018; Cvetnić et al 2007).

The occurrence of tuberculosis in swine is related to the opportunity of contact with tuberculous cattle, humans, and fowl or to the microorganism found in the environment. *M. bovis*-infection is not a frequent cause of tuberculosis in swine in countries where the disease in cattle is controlled and *M. tuberculosis* is just occasionally observed, therefore *M. avium* remains the most frequently isolated among tuberculous-like lesions at pigs (Chambers et al 2018; Straw et al 2006).

The pathogenesis of *Mycobacterium*. The main pathogenic mechanism of bacteria from the *Mycobacterium* genus is based on the ability to survive and multiply within the cells of the mononuclear phagocytic system (MPS) (Sakamoto 2012). Following a receptor-mediated entrance, the mycobacteria inhibit the fusion of the phagosomes with lysosomes, resists the enzymatic attack and multiply, or further can destabilize the lysosomal membrane and translocate to the cell cytosol (Sakamoto 2012). Therefore, the ability of mycobacteria to modulate the MPS-cells organelle compartment is essential for the survival of the bacteria, multiplication and finally for the destruction of these key-cells of the innate immune system cells (Ernst 1998).

This complex intracellular pathogenesis and capacity of mycobacteria to produce such a progressive disease is mediated by a large number of virulence factors. Some of the key pathogenic factors for mycobacterial infection are listed in Table 1.

Table 1
Pathogenic factors involved in mycobacterial infection

<i>Virulence factor</i>	<i>Mechanism of bacterial virulence</i>	<i>Reference</i>
● LAM	●Mycobacteria-adherence to macrophages and inhibition of phagolysosome maturation.	Fratti et al 2003; Torrelles et al 2012
	●Downregulation of IFN-γ transcription	Chan et al 1991
● PIMs	●Immunosuppression by upregulation of IL-10 production	Geijtenbeek et al 2003
	●TB-granuloma development	Gilleron et al 2001
● Cord factor	●Inhibition of phagolysosome maturation	Axelrod et al 2008; Indrigo 2003
	●Induction of cachexia	Perez et al 2000; Welsh et al 2008
	●Oxidative phosphorylation impairment	Kato 1970; Laneelle and Tocanne 1980
● Erp	●T lymphocyte apoptosis	Ozeki et al 1997
	●Intracellular bacterial growth	Berthet 1998
● DIM	●Inhibition of recruitment of macrophages within the inflammatory focus	Cambier et al 2014
	●Survival of bacteria within macrophages	Rousseau et al 2004
	●Mycobacteria-adherence to macrophages	Astarie-Dequeker et al 2009
● Tat pathway	●Phagolysosome fragmentation	Augenstreich et al 2017
	●Antibioresistance	Bhuwan et al 2016; Saint-Joanis et al 2006

LAM - Lipoarabinomannan; Cord factor - Trehalose-6,6'-dimycolate; PIMs - Phosphatidylinositol mannosides; DIM - Phthiocerol dimycocerosate and phenolic glycolipids; Erp - Exported repetitive protein; Tat - Twin-arginine transporter.

In chronic TB cases, the mycobacterial infection is typically associated with a delayed (type IV) hypersensitivity reaction. Within the affected areas and particularly within the local lymph nodes, the infectious process will result in the formation of a granulomatous reaction with massive caseous necrosis and mineralization in advanced stages of disease (Zachary & McGavin 2016).

Porcine Mycobacteriosis as a natural reservoir for bovine tuberculosis. One of the greatest threats in the eradication programs of bovine tuberculosis is the existence of wildlife or feral source of infections, which are difficult to control in both diagnostic or spatial distribution. Therefore, the badger (*Meles meles*) is considered the main wildlife source of bovine TB in the UK, the brushtail possum (*Trichosurus vulpecula*) in Australian and New Zealand, the white-tailed deer (*Odocoileus virginianus*) and elk (*Cervus canadensis*) in North America, the wild and feral pig in Spain and the African buffalo in South Africa (Cousins 2001; Fitzgerald & Kaneene 2013; Thapa et al 2017). The wild boar is considered the single most important bovine TB- a reservoir in southern Europe (Chambers et al 2018; Hermoso de Mendoza et al 2006). Due to the fact that pigs can develop subclinical TB infections, the feral pigs are considered to be one of the main sources of the persistence of tuberculosis in bovines and wildlife in New Zealand (Fitzgerald & Kaneene 2013; Nugent et al 2015). This is despite the complex TB eradication programs which include in most of the herds annual allergic TB skin testing (tuberculin test), complete abattoir surveillance, milk pasteurization and epidemiological monitoring of the movement of bovines between farms (Cousins 2001). The role of pigs (mainly wild pigs) in TB transmission is especially important in certain areas where the prevalence of *M. bovis* infection in pig populations can be close to 100% (Nugent et al 2005).

From an epidemiological perspective, several domestic and wildlife species are considered for tuberculosis as either (1) "maintenance/reservoir hosts" (defined as a species in which TB can persist and can be passed to subsequent generations) or (2) "spillover hosts" (defined as species which are highly sensitive to mycobacterial infection and can transmit the disease but will lost their TB-positive status following removal of the local-main source of TB infection) (Cousins 2001; Fitzgerald & Kaneene 2013). A brief presentation of the main bovine TB reservoirs and their main gross features are presented in Table 2.

Table 2
The main bovine tuberculosis wildlife reservoirs and the main gross features

<i>Mycobacterium species</i>	<i>Reservoir host</i>	<i>Geographical area</i>	<i>Gross lesion distribution</i>	<i>Reference</i>
<i>Mycobacterium bovis</i>	•White-tailed deer	North America	•Submandibular, cranial lymph nodes and respiratory tract	Carstensen & DonCarlos 2011; O'Brien et al 2002
	•European badger	UK and Ireland	•Respiratory tract lymph nodes and subcutaneous tissue	Donnelly et al 2006; Gallagher & Clifton-Hadley, 2000
	•Wild pigs	Spain	•Cranial lymph nodes or systemic dissemination	Cano-Terriza et al 2018; García-Jiménez et al 2013
	•African buffalo	South Africa	•Submandibular and other cranial lymph nodes; respiratory tract	Michel et al 2006; Renwick et al 2007
<i>Mycobacterium caprae</i>	•Wild boar	Spain	•Cranial lymph nodes, mammary gland, joints or systemic dissemination	García-Jiménez et al 2013; Rodríguez et al 2011

A special epidemiological situation of pigs is the "spillback"-status, which is defined as the reciprocal interspecies-transmission, where the TB-infection is transmitted back from the "spillover host" (e.g. pigs) to the maintenance species (e.g. bovines) (Nugent 2011). Evidence to support the role of pigs in the persistence TB and transmission of infection to domestic and wild ruminants includes: (1) common *M. bovis* genotypes isolates from both pigs and ruminants, (2) the persistence of TB infection in pig population despite the lack of a significant ruminant population, and (3) presence of systemic-active lesions which can easily assure the transmission of the infection (Martín-Hernando et al 2007).

Swine as emerging animal model for the study of mycobacterial diseases of humans and bovines. Recently, pigs (especially mini-pigs) emerges as an experimental model in elucidating the TB pathogenesis, host immune response and preclinical anti-TB vaccine efficiency (Gil et al 2010; Ramos et al 2019, 2017; Singh et al 2018). Although less popular than the rodent and guinea pig models (Singh & Gupta 2018; Zhan et al 2017), there are several advantages in using pigs as experimental animal models for human and bovine tuberculosis (Table 3), as: (1) swine are natural hosts for both human and bovine TB-species, thus routine infection is natural and will not require previous immunosuppression (de Lisle 1994; Zimmerman 2012); (2) pigs are readily available and relatively inexpensive as models compared with nonhuman-primates models (as the classical Rhesus macaques or *Cynomolgus* macaque) (Bolin et al 1997; Ramos et al 2017); (3) both physiology and anatomy of swines are highly similar to that of humans (Almond 1996); (4) swine will develop an delayed type (IV-type) of hypersensitivity to mycobacterial infections as humans and bovines, which will determine a particular type of granulomatous lesion and an sensitivity for the tuberculin test (as a routine method for assessment of TB-infectious status) (Muscoplat et al 1975; Nugent et al 2002); (5) large body size which allow repetitive blood and tissue collection with minimal impact on the overall individual-health and well-being (Almond 1996; de Lisle 1994) and (6) the similar pulmonary response to *M. tuberculosis* following respiratory exposure (including the presence of caseation and a fibrous connective tissue as a granuloma-border, latency-period and a positive correlation between a predominant Th1-immune response and limitation of infection) (Gil et al 2010).

Table 3

A Synopsis of the main features of some in vivo animal models used in TB research (Singh et al 2018; Zhan et al 2017; Singh & Gupta 2018; de Lisle 1994)

<i>Animal TB Model</i>	<i>Applications</i>	<i>Advantages</i>	<i>Disadvantages</i>
"Nonhuman primate model" • <i>Macaca fascicularis</i> • <i>Macaca mulatta</i>	<ul style="list-style-type: none"> •Preclinical drug and vaccine evaluation. •Immunological host response to TB infection and pathogenic mechanism. 	<ul style="list-style-type: none"> •Close resemblance to human anatomy, physiology and immunologic response (including morphology of TB-induced lesions) •A good experimental model of HIV (SIV)-tuberculosis coinfection 	<ul style="list-style-type: none"> •High costs •Special husbandry requirements and high-technical expertise required
"Bovine model" • <i>Bos taurus</i>	<ul style="list-style-type: none"> •Preclinical vaccine evaluation. •Immunological host response and TB pathogenic mechanism •Research on susceptibility genes for TB-infection 	<ul style="list-style-type: none"> •A good model for pulmonary tuberculosis and TB susceptibility genes 	<ul style="list-style-type: none"> •Different immune responses (e.g. presence of $\gamma\delta$T cells) leading to a particular evolution and morphology of granuloma. •Few immunological products commercially availability.
"Guinea-pig model" • <i>Cavia porcellus</i>	<ul style="list-style-type: none"> •Immunological host response and TB pathogenic mechanism •Preclinical vaccine and drug evaluation. 	<ul style="list-style-type: none"> •Highly susceptible to TB-infection. •Similar morphology of granulomas with human TB. •Low cost and husbandry requirements. 	<ul style="list-style-type: none"> •TB-latency period not defined. •Different immune responses and susceptibility to Mtb infection. •Few immunological products commercially availability.
"Rodent model" • <i>Mus musculus</i> (mainly C57BL/6 BALB/c C3HeB/FeJ lines) • <i>Rattus norvegicus</i>	<ul style="list-style-type: none"> •Preclinical drug and vaccine evaluation. •Research on susceptibility genes for TB-infection. •Immunological host response to TB infection and pathogenic mechanism of TB 	<ul style="list-style-type: none"> •Low cost and husbandry requirements. •Easy genetical manipulation. •Many immunological products commercially availability. 	<ul style="list-style-type: none"> •TB-latency period not defined. •Different immune responses and morphology of granuloma.
"Mini-Pig model" • <i>Sus scrofa domestica</i>	<ul style="list-style-type: none"> •Preclinical vaccine evaluation. •Immunological host response to TB infection and pathogenic mechanism of TB 	<ul style="list-style-type: none"> •Natural susceptibility to similar mycobacteria species with humans and bovines. •Similar anatomy and philology with humans •Granulomas resemble the morphology of human TB •A good model for pediatric TB. 	<ul style="list-style-type: none"> •More expensive than the rodent and guinea pig model •Few immunological products commercially availability.

Clinicopathological findings of tuberculosis in pigs. The clinical expression of tuberculosis in pigs is generally poor and unspecific. In the early stages, the tuberculous-induced lesions are present to a small extent within the cervical and digestive lymph nodes, typically without any detectable clinical signs (Zimmerman 2012). In the late stages, especially in the disseminated form of tuberculosis, cachexia is often noticed (Ramos et al 2019).

Tuberculosis in swine regularly affects the lymphatic system satellite of the respiratory and digestive system, especially the head lymphatic centers (Chambers et

al 2018). Although the lesions are found in the mesenteric, mandibular and retropharyngeal lymph nodes, histopathological evidenced of TB was present in 38% of the examined lungs, 23% of livers and 13% of spleens analyzed in a large study in wild boars (Martín-Hernando et al 2007). The gross presence of lesions within the above-mentioned viscera is usually rarer (Maxie 2015; Zachary & McGavin 2016). The generalized form of tuberculosis (affecting multiple systems), is also commonly seen in the juvenile wild-boar population (Martín-Hernando et al 2007). In adults wild-boars, systemic dissemination is considered rarer (Bollo et al 2000). In most cases, systemic dissemination is due to the infection with *M. bovis* or *M. tuberculosis*, but it may also result following *M. avium* infection (Cvetnić et al 2007; Polaček & Aleksić-Kovačević 2016; Ramos et al 2019).

The appearance of TB-induced lesions in the lymph nodes of pigs are usually variable in both extension and inflammatory subtype, ranging from pinpoint-size yellowish nodules ("military granulomas") to pea-size caseous granulomas with central mineralization ("calcareous granulomas") (Maxie 2015; Zachary & McGavin 2016). Usually in the military granulomas predominate and are located in the cervical and mesenteric lymph nodes (Brown & Neuman 1979). Based only on gross criteria, a differential diagnosis between lesions caused by mammalian and avian-strains of mycobacteria is not consistently possible. But there are some peculiar features of both granuloma-types (Hibiya et al 2008; Zimmerman et al 2012), in terms of evolution and morphology which may help the distinction in some cases. In the infections produced by *M. avium*, the lymph nodes are hypertrophied, with poorly defined foci of necrosis or suppuration. Focal calcification of the necrotic-caseous foci is rarely observed and usually, there is no obvious tendency of encapsulation (Zimmerman et al 2012). When the granulomatous lesions are produced by the mammalian types of mycobacteria the calcification is usually prominent, and the connective tissue is present at the margins of the granuloma. However, caseous and calcified foci as above described in mesenteric lymph nodes of pigs may also be produced. by mycotic pathogens as *Sporotrichum schenekii* or bacteria as *Nocardia*, *Staphylococcus*, *Actinomyces* or *Actinobacillus* (Pavlas et al 1985).

Histologically, discrete collections of macrophages, epithelioid histiocytes, and multinucleate giant cells with lymphocytes, plasma cells, and fibrosis, occasionally surrounding a central area of necrosis are present within the inflammatory foci induced by mycobacteria. The various admixture of the above-mentioned cell population is responsible for some peculiar features of the TB-granulomas, having a predominant "exudative", "proliferative" or a "mixed" morphology (Hibiya et al 2008). In the case of lymphadenitis produced by the *M. avium-intracellulare* in humans, a sarcoid-like granulomatous reaction, with abundant spindle cell proliferation can develop. Additionally, the presence of tuberculoid granulomas within the lymph nodes could be associated with follicular and paracortical hyperplasia (Leong 2010).

Basically, the histological aspect of a the advanced stage TB case (calcareous tuberculoid granulomas) are similar to those observed in cattle (Chambers et al 2018) and includes three classical components: a central zone of caseous necrosis (often mineralized), rimmed by a second zone consisting of a heterogeneous mixture of macrophages, histiocytes, epithelioid cells and giant cells (occasionally with Langhans-type morphology) and outer peripheral fibrous capsule infiltrated by the above-mentioned cells (Domingo et al 2014; Zachary & McGavin 2016). The presence of neutrophils in TB-induced granulomas is highly variable, and their presence is commonly abundant in cases of rapid multiplication of mycobacteria, affecting especially tissues with high elasticity (as lungs) (Domingo et al 2014; Maxie 2015). Although resistant for usual stains, Ziehl Neelsen stain it can highlight in such granulomas variable numbers of acid-fast bacilli localized within macrophages (and their derivate) or extracellularly within the necrotic debris (Maxie 2015).

Conclusions. In the current review, we briefly discuss and outline the current knowledge on the importance and pathogenesis of tuberculosis and other mycobacterial diseases in

pigs, highlighting the experimental usage of swine in TB-research and the involvement of pigs as a reservoir for bovine TB.

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