Mycobacterium avium paratuberculosis and Mycobacterium avium complex and related subspecies as causative agents of zoonotic and occupational diseases: ESLAMI et al.

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REVIEW ARTICLE

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Mycobacterium avium paratuberculosis and *Mycobacterium avium* complex and related subspecies as causative agents of zoonotic and occupational diseases

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Abstract

Mycobacterium avium complex (MAC) and *Mycobacterium avium paratuberculosis* (MAP) cause zoonotic infections transmitted by birds and livestock herds. These pathogens have remained as serious economic and health threats in most areas of the world. As zoonotic diseases, the risk of development of occupational disease and even death outcome necessitate implementation of control strategies to prevent its spread. Zoonotic MAP infections include Crohn's disease, inflammatory bowel disease, ulcerative colitis, sarcoidosis, diabetes mellitus, and immune-related diseases (such as Hashimoto's thyroiditis). Paratuberculosis has classified as type B epidemic zoonotic disease according to world health organization which is transmitted to human through consumption of dairy and meat products. In addition, MAC causes pulmonary manifestations and lymphadenitis in normal hosts and human immunodeficiency virus (HIV) progression (by serotypes 1, 4, and 8). Furthermore, other subspecies have caused respiratory abscesses, neck lymph nodes, and disseminated osteomyelitis in children and ulcers. However, the data over the occupational relatedness of these subspecies is rare. These agents can cause occupational infections in susceptible herd breeders. Several molecular methods have been recognized as proper strategies for tracking the infection. In this study, some zoonotic aspects, worldwide prevalence and control strategies regarding infections due to MAP and MAC and related subspecies has been reviewed.

KEYWORDS
Crohn's disease, *Mycobacterium avium*, paratuberculosis, zoonosis

1 | CONTEXT

The species of *Mycobacterium avium* has been classified into four subspecies including *M. avium*, *M. hominissuis*, *M. silvaticum*, and *M. paratuberculosis* with a high degree of genetic similarity, but various degrees of infectivity in host species. *M. avium* subsp. *paratuberculosis* (MAP) species is one of the critical pathogens in the livestock industry, a secret threat and a problem in the world's milk herds (Hamilton, Weir, & Haas, 2017b). Recently it has been critically considered due to its tracking in Crohn's disease (CD) in human and millions of dollars of economic losses and trade restrictions on the livestock industry in many countries (Jarand, Davis, Cowie, Field, & Fisher, 2016).

Paratuberculosis in animals, also known as Jones disease is a chronic, infectious, and often fatal colon granulomatous infection (Eslami, 2011). That was first identified in cattle and subsequently in sheep and goats (Grant, 2005). Paratuberculosis bacilli can be colonized in most animals including, domestic or wild ruminants, wild carnivores, laboratory animals, and nonhuman primates (Waddell et al., 2008).

M. avium, belonging to the slow-growing group of mycobacteria, causes zoonotic disease which develops in humans. Among the opportunistic pathogens, the term *M. avium*, *M. intracellulare*, and *M. scrofulaceum* (MAIS) was previously referred to as a group of slow-growing mycobacteria, seeming very similar in appearance and in some cases, thus difficult to be subtracted from each other (Tortoli, 2012). Recently, the term MAIS have not been used according to the results of techniques such as nucleic acid hybridization, antigenic analysis, and the ability of the organism to metabolize urea, in which *M. scrofulaceum* is easily distinguishable from *M. avium* and *M. intercellular*. The word "MAC" stands for the *M. avium* complex that contains the two main species *M. avium* and *M. intracellulare* and several other subspecies in this complex (*M. chimaera* and *M. lepraemurium*) also isolated from human and considered as zoonotic agents (Hamilton et al., 2017b; Jarand et al., 2016)

2 | INFECTION OF *M. AVIUM* SUBSP. *PARATUBERCULOSIS* IN HUMANS

The pathogenicity of paratuberculosis in humans depends on age, genetics, environmental contamination, health status, geographical location, dietary habits, the presence of specific microorganisms, mechanisms of disease, medication, and host immune responses. The two major clinical manifestations of paratuberculosis in human include inflammatory bowel disease (IBD) and autoimmune diseases (asthma, insulin-dependent diabetes mellitus, sarcoidosis, rheumatoid arthritis, multiple sclerosis, and celiac disease (Grant, 2005; Naser, Sagramsingh, Naser, & Thanigachalam, 2014). A group of chronic gastrointestinal disorders with unspecified agents are classified into three groups including ulcerative colitis, CD, and IBD based on clinical findings (Pierce, 2018).

3 | CROHN'S DISEASE

Dolseil in 1913, identified a similar pathology between the intestinal tissue of patients with intestinal tuberculosis CD in men and paratuberculosis in ruminants (Jones disease), demonstrating a relationship between the bacilli and CD several years later (Alcedo, Thanigachalam, & Naser, 2016). Findings highlight the disease by observation of lack of similarity between isolates from cows and those from human populations and no maternal/vertical transmission of *Mycobacterium avium paratuberculosis*. It seems that the susceptibility rate to the bacterium is not the same in various regions among populations. CD affects 1–2 million people worldwide (Atreya et al., 2014). It is currently believed that CD is a polygenic disease in which MAP is one of the causative agents along with other agents such as pathogens (bacteria, viruses, and fungi), environmental factors and inappropriate immune response in genetically susceptible hosts (McNees, Markesich, Zayyani, & Graham, 2015). CD as a systemic illness has been identified with the initial symptoms of chronic otitis media that may occur in the mouth from the gastrointestinal tract in any area. CD pathogenicity mechanism is similar to ulcerative colitis. However, due to inadequate inactivation of intestinal protease and an excess of glycosidases, degradation of the mucosal layer leads to damage to the intestinal duct. The formation of inflammatory granulomatosis is a result of increased lumen penetration of the entire intestine into antigens and accumulation of macrophages. The disease begins with symptoms of abdominal pain, diarrhea, lethargy and weight, night sweats, vomiting, skin rash, microcytic anemia, oral ulcer, and arthralgia, and in some cases peritonitis, appendicitis, and perforation of the ulcerative ileum. CD is a progressive and unbreakable disease that occurs throughout the world (especially in industrialized countries; Baumgart & Sandborn, 2012).

Based on studies, there is evidence that the etiology of the CD (in humans) and Jones disease (in the animal) have been confirmed, which include bacterial survival in commercial pasteurization methods, MAP detection in the tissues and blood of contaminated patients, increased antibody levels in sera samples of patients in the face of bacterial antigens, bacterial tracing in infected mothers, NOD2/CARD15 mutations, and response to antibiotic therapy by the macrolide family (Davis & Park, 2018; Kuenstner et al., 2017). On the other hand, there is a lack of similarities between the genotypes of bovine and human isolates, the isolation of bacteria from individuals without CD, the lack of sufficient evidence to confirm the consumption of contaminated food by patients, and the lack of transmission of bacteria from the infected mother and inactivation of bacteria causing the CD which highlight the agent existence (Mendoza, Lana, & Díaz-Rubio, 2009). The transmission of paratuberculosis through a food chain or contaminated water resources, especially pasteurized milk, and unheated meat to humans, has caused animals as reservoirs to play an important role in the possible transmission of disease to humans. The difference in the prevalence of CD is seen in countries (Europe and the United States) and even in different ethnic groups, with about 170 and 40 per 100,000 children and adults in the North America and Europe, respectively. Although in Canada, Europe, and the United States the disease is often diagnosed in women, there is no evidence of its association with specific sex (Dirac et al., 2012; Mendoza et al., 2009; Shafiei, 2018 #303).

Based on clinical findings and diagnostic techniques, CD is associated with ulcerative colitis in humans and Jones disease in primates, but there are also exceptions including the main problem with paratuberculosis is the infection of the gastrointestinal tract at any time and bacterial survival for 2–10 years without causing obvious symptoms of infection in the animal. On the other hand, during the subclinical phase, the intermittent excretion of bacteria through milk and stool is considered as a major source for transferring bacilli among the herds (Hermon-Taylor et al., 2000b).

As the main route of transmission, gastrointestinal or fecal–oral transmission is mainly contaminated by oral ingestion of water or food contaminated with the feces of adult infected animals. Other ways of spreading the disease between the herd and human populations are the respiratory transmission following inhalation of dust caused by inert material (pasture or fertilizer) and the transient transmission through the semen and sperm fluid of the male livestock contaminated with the sensitive members of the herd. Evidence suggests that vertical transmission through intrauterine and endocrine glands (milk, colostrum) is also referred to as other routes (Keating, Daly, & Practice, 2013). Paratuberculosis is prevalent in cattle, occurring in four stages: latent, subclinical, clinical, and advanced, which in the advanced phase, the quick death of the animal will be the outcome. *M. avium* subsp. *avium* causes three major clinical features in humans including pulmonary disease and lymphadenitis in healthy subjects and disseminated disease in human immunodeficiency virus (HIV)-infected patients (Hamilton, Ahmed, Toze, & Haas, 2017a; Maekawa et al., 2011). Furthermore, these agents caused infection following patient' organs transplantation (Chiers et al., 2012). The causative agent was identified as an occupational infectious bacterium in roof-harvested rainwater in Queensland, Australia (Lara et al., 2011). In addition, high soil exposure (≥2/weeks), determined as a significant risk factor (Yong, Choi, Lee, Whang, & Shin, 2011). It has been also reported in birds, pig's wild boars, elephants, horse (*M. silvaticum*), and dog (*M. hominissuis*; Escobar-Escamilla et al., 2014; Nunes-Costa, Alarico, Dalcolmo, Correia-Neves, & Empadinhas, 2016; Yong et al., 2011). Therefore, there is the possibility of incidence of zoonotic and occupational infections by these subspecies.

4 | OTHER MAC SUBSPECIES

Other subspecies of MAC based on 16s rRNA sequencing mostly include *M. chimaera* (or MAC-A serovar from human respiratory system), *M. colombiense* (from children lymph nodes), *M. arosiense* (or MAC-X serovar from systemic osteomyelitis of HIV-infected children), *M. indicus pranii* (MIP or Mw), *M. vulneris* (isolated from ulcers), *M. xenopi*, and *M. lepraemurium* which caused infections less common in humans. Because of nonoptimization of diagnostic methods, these subspecies are underestimated (Biet & Boschiroli, 2014; Lamont, Bannantine, Armién, Ariyakumar, & Sreevatsan, 2012; Rosenfeld & Bressler, 2010). They are mostly isolated from sputum and other pulmonary specimens. It is generally believed that vast environmental sources such as swimming pools, tap waters, potting, and aquaria act as infectious niche.

5 | EPIDEMIOLOGY OF MAP AND MAC

MAC mainly causes the infection in pigs and poultry. Other hosts include cows, sheep, goats, deer, and antelopes, bagpipes, primates, and horses which can transfer the infection to humans. *M. avium*, which is also widely isolated from the environment, such as water, soil, air, and unpasteurized milk can be as a primary source for bacterial spread (Grant, 2005; Waddell et al., 2008). The differentiation between *avium* and *intracellulare* subspecies is difficult by phenotypic methods and necessitates techniques that are usually only available in reference laboratories, and therefore, these species are often reported as MAC (Norton, Johnson, Jones, & Heuer, 2010). In humans, MAC is one of the opportunistic pathogens causing swollen neck lymph nodes or scrofula (especially in children) and also causes pulmonary infections in older individuals. These species are the common cause of the opportunistic mycobacterial disease associated with AIDS, which occurs in 30–50% of patients with AIDS in the United States and Europe, and lead to the diffused or miliary tuberculosis (Gardner et al., 2011). Almost all cases related to AIDS are due to strains which are genetically related to *M. avium*. In most cases, the infection is widely disseminated in the body. In these patients, the organism can be isolated from the blood, bone marrow and stool. *M. avium* can survive in the soil for up to 4 years, although sensitive to sunlight and ultraviolet radiation.

On the other hand, paratuberculosis (Jones disease) has spread almost worldwide, especially in developing countries, as an endemic disease and a major problem in many livestock production systems, zoo enclosed animals, and wildlife animals. The disease report was only from 6 to 12 countries around the world by 1997, but there are currently numerous reports of occurrence, epidemiology, potential zoonotic condition, and biological origins (by molecular methods) from all continents. Epidemiological studies have suggested that the risk of infection in males, black race humans, near-equator countries, rural areas, and occupations associated with soil and fertilizer is higher (Carvalho, Pietralonga, Schwarz, Faria, & Moreira, 2012).

The MAP can be controlled, but early detection and proper diagnosis are pivotal to prevent its transmission among animals (Cho et al., 2012). The jones disease causes death without estimation and called a silent killer. Therefore, some critical points have been considered in controlling studies in recent decades such as its epidemiology, identifying sources of infection, and the process of the disease spreading (Chiers et al., 2012; Davis & Park, 2018; Lara et al., 2011; Yong et al., 2011), some of which have been implemented in Sweden and some states of Australia due to the use of valid reporting systems and severe control measures as the only areas free of the Jones disease in the world.

Reports of MAP tracing in commercially available pasteurized milk from some countries such as the United States (8.2%), England (1.7%), Argentina (86.2%), and India (67%; Garcia & Shalloo, 2015) highlighted the possibility of association of paratuberculosis and CD with contaminated food. There is still no evidence of animal to human transmission, however, control of the disease in livestock, as the key to the reduction of CD in humans is essential (Li, Katani, Schilling, & Kapur, 2016).

The collected data on the epidemiology and ecology of livestock in mild and temperate climates suggest that bovine paratuberculosis infection is rare in tropical and subtropical areas. Therefore, the infection may be due to the predominantly cows in temperate and wet climates to the above areas. Studies have also shown that the age-specific factors such as pathogenicity of strain, severity, and persistence of infection, sex, race, herd size, and stressors (labor, malnutrition, transportation) in the development and evolution of the disease and effective in clinical form. The most reliable method for detecting paratuberculosis-infected animals is the culture of organisms from various clinical specimens such as blood, milk, lymph nodes, tissue (intestine, liver, testis, uterus, and bladder), and especially fecal specimens.

Estimates of annual economic losses associated with ion disease in the clinical and subclinical stage among dairy herds have shown significant effects on national, regional and agricultural levels. The largest economic impact of Jones disease is on livestock industry, especially dairy cattle, where estimates of losses caused by reduced immature slaughter, carcass weight loss, weight loss, reduced milk production, and infertility in animals with high fecal excretion rates are high in the United States alone ($250 million a year; Bates, O'Brien, Liggett, & Griffin, 2018; Machado et al., 2018).

Over 100 years old, the prevalence of bovine paratuberculosis has grown from 55% to 10% in the 1990s, based on the diversity of the prevalence in the European countries (Li et al., 2016). The prevalence rate of bacilli prevalence at herd and livestock levels in European countries is 2–50% or higher. In Switzerland, this is 1.7–2.7%, Denmark 47%, Austria 19%, Belgium 18%, Ireland 9.5%, Italy 14.14% 8.2%, and in France is estimated to be 6.2–6.6% (Dore et al., 2012; Smith et al., 2016). In contrast, its rate in the United States has been estimated at the herd level of 21–93% and at least 2.9% for each dairy cattle (McKenna, Keefe, Tiwari, VanLeeuwen, & Barkema, 2006). National Animal Health Control System (NAHMS) reports in the United States indicate that the prevalence of jones disease has risen from 21% in 1996 to 93% in 2006, with 70% of dairy herds and 10–5% of calves contaminated with the bacilli (Ahlstrom et al., 2015; Gümüşsoy, Ica, Abay, Aydin, & Hizlisoy, 2015; Slater et al., 2016b).

The first report of bovine paratuberculosis in African countries dates back to 1923. According to the OIE database on animal health, from 1980 until today, it appears that in most African countries, the disease is endemic or sporadic, the prevalence of the disease in Egypt has been reported 45.2% and 9%. The frequency of the disease is also available in several Asian countries, such as Jordan 65%, India 25–25% (Dirac et al., 2012), Korea 16.4%, Pakistan 76.6%, Turkey 4.3–7.2%, and Cyprus 9/0%. The most important step in solving the paratuberculosis problem should be the implementation of surveillance measures to control the disease and, if possible, to prevent contact with predisposed and infected young animals. To prevent the spread of infection, a close cooperation between farmers, livestock breeders, and health inspectors is needed to protect animals susceptible to irritable bowel syndrome by removing an infected animal with a test-slaughter solution and vaccination (Slater et al., 2016a).

In the area of protecting animals susceptible to MAP, effective treatment of infections involves a variety of functions, including the quarantination of newly born young calves in a separate site, increasing the health level of calves, young animals feeding with MAP-free milk or supplements, control of contaminated water, and food in separated animals, and the feeding of calves in fields free from animal waste. Control programs in dairy cattle require the slaughter of infected animals as the main health action to prevent infection in young calves. Based on reports of control measures in different countries, the test-slaughtering strategy is based on the results of three stool culture tests, ELISA, and eventually molecular techniques that can be monitored, regardless of its economic constraints, for administering in small herds, more than a total of 7 years for complete elimination of the disease.

In spite of extensive control efforts in different countries, paratuberculosis remains an insoluble problem for the scientific community of veterinary medicine, as they have not yet come up with a single opinion to reach a more proper strategy to deal with this disease, which is to some extent extended to the incubation period, the lack of adequate knowledge for the precise differentiation of strains, the limited knowledge regarding bacterial pathogens, and the inadequacy of present vaccines. Studies have shown that killed and subjunctive vaccines are effective in preventing the establishment of a stable infection and limiting the progression of the disease, but they have not been completely successful in infection prevention.

6 | THE *M. AVIUM* TRANSMISSION

The contaminated environment, especially the soil and infected bed, is the most important source of transmission of infection to noninfected animals (Bauman et al., 2017). The most important route of infection transmission in birds is through food and contaminated water (oral–fecal transmission). After ingestion, the microorganism disseminates throughout the bird's body and subsequently can be spread by feces after propagation. If the bacterium is inhaled, lung injuries may develop and skin invasion may also appear. Although MAC spread through contaminated eggs may occur, this is not a common route in the chickens hatching from the eggs (Bauman et al., 2017). The development and spread of the bird's tuberculosis do not occur by industrial poultry through birds carcasses used to produce meat powder. Cannibalism may also be involved in the transmission of the disease. Detection of tuberculosis in birds is difficult due to the various and uncertain signs, the length of the latency, the lack of appropriate serological tests, and the difficulty in the agent's culture in vitro (Ahlstrom et al., 2016). MAC in birds has been limited to a small number of studies worldwide. Therefore, the frequency and information about of MAC infection among birds are uncertain.

7 | MOLECULAR TRACKING OF DISEASE

The transmission and epidemiology of MAP and MAC have been investigated by several molecular methods. However, the application of combined typing methods has been highlighted to achieve more accurate results. Pulsed-field gel electrophoresis has been used to this aim, but the technique is time-consuming and laborious. Multivariate tandem repeat analysis, IS900 restriction fragment length polymorphism (IS900RFLP) analysis and mycobacterial interspersed repetitive unit–variable-number tandem-repeat typing have also demonstrated proper results in the tracking of disease transmission and identification of zoonotic subspecies (Garvey, 2018; Kennedy & Benedictus, 2001; Mikkelsen, Jungersen, & Nielsen, 2009).

8 | CONTROL AND PREVENTION STRATEGIES

Control strategies for prevention of the infection can be mostly classified as (a) discard or cleansing old or dirty equipment, (b) avoid moving and migration of birds to suspected and infected places and import of suspected herds, (c) removing old flocks and burning carcasses, (d) buying new birds from specific and nonpolluted places, (e) reducing the stress of birds as an important factor in increasing bacterial excretion and disease evolution by reducing the density of birds and providing adequate ventilation and the use of vitamin and mineral supplements, (f) repeated disinfection of the birds and livestock holding places, (g) monitoring the birds and livestock in the field by testing tuberculin and agglutination, (h) quarantine new birds for at least two months and conduct tuberculin testing, (i) even if there is an infected bird, all herds should be removed, and disinfection and removal of all equipment and even the Fulton herd must be fulfilled and (j) vaccination of birds and herd (Abdellrazeq et al., 2018; Cohn, 1997). However, the herd and livestock status and national conditions are critical determinants of control plans.

9 | VACCINATION

There are no commercial vaccines for use against MAP and MAC. Several live and killed experimental vaccines have been evaluated to protect poultry against the disease. The most protective vaccine was evaluated with *M. intracellulare* serovar 6 after oral use with 70% protection after muscular injection with *M. avium*. In addition, recombinant vaccines and subunits have been experimentally tested. Vaccination reduces the number of injuries and bacilli but does not prevent the infection. Induction of CD8+ and CD4+ responses are critical for the eradication of intracellular infection, though limited cell apoptosis has been exhibited for intracellular bacteria (Hermon-Taylor et al., 2000a; Velaz-Faircloth, Cobb, Horstman, Henry, & Frothingham, 1999).

10 | CONCLUSION

The rate of MAP and MAC has remained high in most areas of the world. Both agents cause zoonotic infections with a wide range of hosts. In addition, related subspecies of MAC have been isolated from clinical origins and environment. As zoonotic diseases, the risk of development of occupational diseases and even death outcome necessitate implementation of control strategies to prevent their spread. Molecular epidemiological studies are useful to track specific sources. Other subspecies of MAC based on 16s rRNA sequencing mostly include *M. chimaera* (or MAC-A serovar from human respiratory system), *M. colombiense* (from children lymph nodes), *M. arosiense* (or MAC-X serovar from systemic osteomyelitis of HIV-infected children), *M. indicus pranii* (MIP or Mw), *M, vulneris* (isolated from ulcers), *M. xenopi*, and *M. lepraemurium* which caused infections less common in humans.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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REFERENCES

Abdellrazeq, G. S., Elnaggar, M. M., Bannantine, J. P., Park, K. T., Souza, C. D., Backer, B., … Davis, W. C. (2018). A Mycobacterium avium subsp. paratuberculosis relA deletion mutant and a 35 kDa major membrane protein elicit development of cytotoxic T lymphocytes with ability to kill intracellular bacteria. *Veterinary Research*, *49*(1), 53–55.

Ahlstrom, C., Barkema, H. W., Stevenson, K., Zadoks, R. N., Biek, R., Kao, R., … De Buck, J. (2015). Limitations of variable number of tandem repeat typing identified through whole genome sequencing of Mycobacterium avium subsp. paratuberculosis on a national and herd level. *BMC Genomics*, *16*, 161.

Ahlstrom, C., Barkema, H. W., Stevenson, K., Zadoks, R. N., Biek, R., Kao, R., … De Buck, J. (2016). Genome-wide diversity and phylogeography of mycobacterium avium subsp. paratuberculosis in Canadian dairy cattle. *PLOS One*, *11*(2), e0149017.

Alcedo, K. P., Thanigachalam, S., & Naser, S. A. (2016). RHB-104 triple antibiotics combination in culture is bactericidal and should be effective for treatment of Crohn's disease associated with Mycobacterium paratuberculosis. *Gut Pathogens*, *8*(1), 32.

Atreya, R., Bülte, M., Gerlach, G.-F., Goethe, R., Hornef, M. W., Köhler, H., … Weiss, S. (2014). Facts, myths, and hypotheses on the zoonotic nature of Mycobacterium avium subspecies paratuberculosis. *International Journal of Medical Microbiology*, *304*(7), 858–867.

Bates, A., O'brien, R., Liggett, S., & Griffin, F. (2018). The effect of subclinical infection with Mycobacterium avium subsp. paratuberculosis on milk production in a New Zealand dairy herd. *BMC Veterinary Research*, *14*(1), 93–93.

Bauman, C. A., Jones-Bitton, A., Ahlstrom, C., Mutharia, L., De Buck, J., Jansen, J., … Menzies, P. (2017). Identification of Mycobacterium avium subspecies paratuberculosis strains isolated from dairy goats and dairy sheep in Ontario, Canada. *Canadian journal of veterinary research*, *81*(4), 304–307.

Baumgart, D. C., & Sandborn, W. J. (2012). Crohn's disease. *The Lancet*, *380*(9853), 1590–1605.

Biet, F., & Boschiroli, M. L. (2014). Non-tuberculous mycobacterial infections of veterinary relevance. *Research in Veterinary Science*, *97*, S69–S77.

Carvalho, I. A., Pietralonga, P. A. G., Schwarz, D. G. G., Faria, A. C. S., & Moreira, M. A. S. (2012). Short communication: Recovery of viable

Mycobacterium avium subspecies paratuberculosis from retail pasteurized whole milk in Brazil. *Journal of Dairy Science*, *95*(12), 6946–6948.

Chiers, K., Deschaght, P., De Baere, T., Dabrowski, S., Kotlowski, R., De Clercq, D., … Vaneechoutte, M. (2012). Isolation and identification of Mycobacterium avium subspecies silvaticum from a horse. *Comparative Immunology, Microbiology and Infectious Diseases*, *35*(4), 303–307.

Cho, J., Tauer, L. W., Schukken, Y. H., Gómez, M. I., Smith, R. L., Lu, Z., & Grohn, Y. T. (2012). Economic analysis of Mycobacterium avium subspecies paratuberculosis vaccines in dairy herds. *Journal of Dairy Science*, *95*(4), 1855–1872.

Cohn, D. L. (1997). Prevention strategies for Mycobacterium avium-intracellulare complex (MAC) infection. A review of recent studies in patients with AIDS. *Drugs*, *54*(Suppl 2), 8–15. discussion 28-19

Davis, W. C., & Park, K. T. (2018). Progress towards control of a Mycobacterial pathogen, Mycobacterium aviumsubsp. paratuberculosis, the causative agent of Johne's disease in cattle and humans. *Journal of Food Hygiene and Safety*, *33*(4), 221–228.

Dirac, M. A., Horan, K. L., Doody, D. R., Meschke, J. S., Park, D. R., Jackson, L. A., … Cangelosi, G. A. (2012). Environment or host? A case–control study of risk factors for Mycobacterium avium complex lung disease. *American Journal of Respiratory and Critical Care Medicine*, *186*(7), 684–691.

Doré, E., Paré, J., Côté, G., Buczinski, S., Labrecque, O., Roy, J. P., & Fecteau, G. (2012). Risk factors associated with transmission of Mycobacterium avium subsp. paratuberculosis to calves within dairy herd: A systematic review. *Journal of Veterinary Internal Medicine*, *26*(1), 32–45.

Escobar-Escamilla, N., Ramírez-González, J. E., González-Villa, M., Torres-Mazadiego, P., Mandujano-Martínez, A., Barrón-Rivera, C., … Cortés-Ortíz, I. A. (2014). Hsp65 phylogenetic assay for molecular diagnosis of nontuberculous mycobacteria isolated in Mexico. *Archives of Medical Research*, *45*(1), 90–97.

Eslami, M. (2011). Comparison of culture and PCR methods for the detection of John's disease in milk samples. *Journal of Animal and Veterinary Advances*, *10*(5), 614–618.

Garcia, A. B., & Shalloo, L. (2015). Invited review: The economic impact and control of paratuberculosis in cattle. *Journal of Dairy Science*, *98*(8), 5019–5039.

Gardner, I. A., Nielsen, S. S., Whittington, R. J., Collins, M. T., Bakker, D., Harris, B., … Eda, S. (2011). Consensus-based reporting standards for diagnostic test accuracy studies for paratuberculosis in ruminants. *Preventive Veterinary Medicine*, *101*(1-2), 18–34.

Garvey, M. (2018). Mycobacterium avium subspecies paratuberculosis: A possible causative agent in human morbidity and risk to public health safety. *Open Veterinary Journal*, *8*(2), 172–181.

Grant, I. R. (2005). Zoonotic potential of Mycobacterium avium ssp. paratuberculosis: The current position. *Journal of Applied Microbiology*, *98*(6), 1282–1293.

Gümüşsoy, K., Ica, T., Abay, S., Aydin, F., & Hizlisoy, H. (2015). Serological and molecular diagnosis of paratuberculosis in dairy cattle. *Turkish Journal of Veterinary and Animal Sciences*, *39*(2), 147–153.

Hamilton, K. A., Ahmed, W., Toze, S., & Haas, C. N. (2017a). Human health risks for Legionella and Mycobacterium avium complex (MAC) from potable and non-potable uses of roof-harvested rainwater. *Water Research*, *119*, 288–303.

Hamilton, K. A., Weir, M. H., & Haas, C. N. (2017b). Dose response models and a quantitative microbial risk assessment framework for the Mycobacterium avium complex that account for recent developments in molecular biology, taxonomy, and epidemiology. *Water Research*, *109*, 310–326.

Hermon-Taylor, J., Bull, T. J., Sheridan, J. M., Cheng, J., Stellakis, M. L., & Sumar, N. (2000a). Causation of Crohn's disease by Mycobacterium avium subspecies paratuberculosis. *Canadian Journal of Gastroenterology*, *14*(6), 521–539.

Hermon-Taylor, J., Bull, T. J., Sheridan, J. M., Cheng, J., Stellakis, M. L., & Sumar, N. (2000b). Causation of Crohn's disease by Mycobacterium avium subspecies paratuberculosis. Canadian. *Journal of Gastroenterology and Hepatology*, *14*(6), 521–539.

Jarand, J., Davis, J. P., Cowie, R. L., Field, S. K., & Fisher, D. A. (2016). Long-term follow-up of Mycobacterium avium complex lung disease in patients treated with regimens including clofazimine and/or rifampin. *Chest*, *149*(5), 1285–1293.

Keating, M. R., & Daly, J. S. (2013). Nontuberculous mycobacterial infections in solid organ transplantation. *American Journal of Transplantation*, *13*(s4), 77–82.

Kennedy, D. J., & Benedictus, G. (2001). Control of Mycobacterium avium subsp. paratuberculosis infection in agricultural species. *Revue scientifique et technique (International Office of Epizootics)*, *20*(1), 151–179.

Kuenstner, J. T., Naser, S., Chamberlin, W., Borody, T., Graham, D. Y., McNees, A., … Kuenstner, L. (2017). The consensus from the Mycobacterium avium ssp. paratuberculosis (MAP) conference 2017. *Frontiers in Public Health*, *5*, 208.

Lamont, E. A., Bannantine, J. P., Armién, A., Ariyakumar, D. S., & Sreevatsan, S. (2012). Identification and characterization of a spore-like morphotype in chronically starved Mycobacterium avium subsp. paratuberculosis cultures. *PLOS One*, *7*(1), e30648.

Lara, G. H. B., Ribeiro, M. G., Leite, C. Q. F., Paes, A. C., Guazzelli, A., Silva, A. V., … Listoni, F. J. P. (2011). Occurrence of Mycobacterium spp. and other pathogens in lymph nodes of slaughtered swine and wild boars (*Sus scrofa*). *Research in Veterinary Science*, *90*(2), 185–188.

Li, L., Katani, R., Schilling, M., & Kapur, V. (2016). Molecular epidemiology of Mycobacterium avium subsp. paratuberculosis on dairy farms. *Annual review of animal biosciences*, *4*, 155–176.

Machado, G., Kanankege, K., Schumann, V., Wells, S., Perez, A., & Alvarez, J. (2018). Identifying individual animal factors associated with Mycobacterium avium subsp. paratuberculosis (MAP) milk ELISA positivity in dairy cattle in the Midwest region of the United States. *BMC Veterinary Research*, *14*(1), 28–28.

Maekawa, K., Ito, Y., Hirai, T., Kubo, T., Imai, S., Tatsumi, S., … Mishima, M. (2011). Environmental risk factors for pulmonary Mycobacterium avium-intracellulare complex disease. *Chest*, *140*(3), 723–729.

McKenna, S. L. B., Keefe, G. P., Tiwari, A., VanLeeuwen, J., & Barkema, H. W. (2006). Johne's disease in Canada part II: Disease impacts, risk factors, and control programs for dairy producers. *The Canadian Veterinary Journal*, *47*(11), 1089–1099.

McNees, A. L., Markesich, D., Zayyani, N. R., & Graham, D. Y. (2015). Mycobacterium paratuberculosis as a cause of Crohn's disease. *Expert Review of Gastroenterology & Hepatology*, *9*(12), 1523–1534.

Mendoza, J. L., Lana, R., & Díaz-Rubio, M. (2009). Mycobacterium avium subspecies paratuberculosis and its relationship with Crohn's disease. *World Journal of Gastroenterology*, *15*(4), 417.

Mikkelsen, H., Jungersen, G., & Nielsen, S. S. (2009). Association between milk antibody and interferon-gamma responses in cattle from Mycobacterium avium subsp. paratuberculosis infected herds. *Veterinary Immunology and Immunopathology*, *127*(3-4), 235–241.

Naser, S. A., Sagramsingh, S. R., Naser, A. S., & Thanigachalam, S. (2014). Mycobacterium avium subspecies paratuberculosis causes Crohn's disease in some inflammatory bowel disease patients. *World Journal of Gastroenterology*, *20*(23), 7403.

Norton, S., Johnson, W. O., Jones, G., & Heuer, C. (2010). Evaluation of diagnostic tests for Johne's disease (Mycobacterium avium subspecies paratuberculosis) in New Zealand dairy cows. *Journal of Veterinary Diagnostic Investigation*, *22*(3), 341–351.

Nunes-Costa, D., Alarico, S., Dalcolmo, M. P., Correia-Neves, M., & Empadinhas, N. (2016). The looming tide of nontuberculous mycobacterial infections in Portugal and Brazil. *Tuberculosis*, *96*, 107–119.

Pierce, E. S. (2018). How did Lou Gehrig get Lou Gehrig's disease? Mycobacterium avium subspecies paratuberculosis in manure, soil, dirt, dust and grass and amyotrophic lateral sclerosis (motor neurone disease) clusters in football, rugby and soccer players. *Medical Hypotheses*, *119*, 1–5.

Rosenfeld, G., & Bressler, B. (2010). Mycobacterium avium paratuberculosis and the etiology of Crohn's disease: A review of the controversy from the clinician's perspective. *Canadian Journal of Gastroenterology*, *24*(10), 619–624.

Shafiei, M., Ghasemian, A., Eslami, M., Nojoomi, F., Rajabi-Vardanjani, H. (2018). Risk factors and control strategies for silicotuberculosis as an occupational disease. *New Microbes and New Infections*. https://doi.org/10.1016/j.nmni.2018.11.002

Slater, N., Mitchell, R. M., Whitlock, R. H., Fyock, T., Pradhan, A. K., Knupfer, E., … Louzoun, Y. (2016a). Impact of the shedding level on transmission of persistent infections in Mycobacterium avium subspecies paratuberculosis (MAP). *Veterinary Research*, *47*, 38–38.

Slater, N., Mitchell, R. M., Whitlock, R. H., Fyock, T., Pradhan, A. K., Knupfer, E., … Louzoun, Y. (2016b). Impact of the shedding level on transmission of persistent infections in Mycobacterium avium subspecies paratuberculosis (MAP). *Veterinary Research*, *47*, 38.

Smith, R. L., Gröhn, Y. T., Pradhan, A. K., Whitlock, R. H., Van Kessel, J. S., Smith, J. M., … Schukken, Y. H. (2016). The effects of progressing and nonprogressing Mycobacterium avium ssp. paratuberculosis infection on milk production in dairy cows. *Journal of Dairy Science*, *99*(2), 1383–1390.

Tortoli, E. (2012). Epidemiology of cervico-facial pediatric lymphadenitis as a result of nontuberculous mycobacteria. *International Journal of Mycobacteriology*, *1*(4), 165–169.

Velaz-Faircloth, M., Cobb, A. J., Horstman, A. L., Henry, S. C., & Frothingham, R. (1999). Protection against Mycobacterium avium by DNA vaccines expressing mycobacterial antigens as fusion proteins with green fluorescent protein. *Infection and Immunity*, *67*(8), 4243–4250.

Waddell, L. A., Rajić, A., Sargeant, J., Harris, J., Amezcua, R., Downey, L., … McEwen, S. A. (2008). The zoonotic potential of Mycobacterium avium spp. paratuberculosis: A systematic review. *Canadian Journal of Public Health*, *99*(2), 145–155.

Yong, H., Choi, G.-E., Lee, B. S., Whang, J., & Shin, S. J. (2011). Disseminated infection due to Mycobacterium avium subsp. avium in an Asian elephant (*Elephas maximus*). *Journal of Zoo and Wildlife Medicine*, *42*(4), 743–746.

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