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A review on paratuberculosis (*Mycobacterium avium* subspecies *paratuberculosis*) in domestic animals

S.S.H. Bukhari[1*], A.M.Gill[2], E. Mahboob[3], M. Moazam[4], S. Ali[5], M.U. Farooq[6]

[1] *Saeed Veterinary Medical Clinic, Attock, 43600, Pakistan*

[2] *Poultry Disease Diagnostic Laboratory, Bahawalnagar, 63100, Pakistan*

[3] *Department of Pathology, University of Agriculture, Faisalabad, 38000, Pakistan*

[4] *Civil Veterinary Hospital, Bahawalpur, 63100, Pakistan*

[5] *Civil Veterinary Dispensary 5/11L, Chichawatni, 57200, Pakistan*

[6] *Civil Veterinary Dispensary Karyal, Sahiwal, 57000, Pakistan*

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Abstract

Paratuberculosis is a production limiting disease of ruminants, also causes infection in non-ruminants and birds; caused by *Mycobacterium avium* subspecies *paratuberculosis (MAP),* characterized by chronic intestinal inflammation, intermittent diarrhea, progressive weight loss and ultimately death of animal. In a herd; vertical as well as horizontal transmission occurs as a result of fecal contamination, through colostrum or common feeding and watering. It is diagnosed by clinical examination and through certain biochemical and serological tests such as Polymerase chain reaction, Enzyme linked immunosorbent assay and Ager gel immunodiffusion test. It is considered as non-curable disease and can be controlled by vaccine, proper management and culling of infected animals.

* **Corresponding Author:** S.S.H. Bukhari ✉ dr.saadshah2622@gmail.com

Introduction

Paratuberculosis-A Production Limiting Disease

Paratuberculosis is a fatal disease of gastro intestinal tract that is characterized by emaciation, cachexia and intermittent watery diarrhea leading to death in animals. It is a disease of compound stomach animals viz sheep, goat, cattle, buffalo, camel and wild ruminants as well as some simple stomach animals like primates, pigs, dogs, horses and birds (Manning and Collins, 2001; Verma, 2013) it also has been reported in elk, bison, red deer and bighorn sheep (Mihajlovic *et al.,* 2011; Forde *et al.,* 2012) but rat and guinea pig are resistant to this infection. It is caused by obligate, acid fast, anaerobic, intracellular bacteria named as *Mycobacterium avium* subspecies *paratuberculosis (MAP)* that gradually damages the ileum and ileocecal valve of small intestine (Rodrick *et al.,* 1984: Ayele *et al.,* 2001; Naser *et al.*, 2007). First time, Paratuberculosis was reported by Heinrich Albert Johns and Frothingam in 1895 in Germany (Ryan and Campbell, 2006) named as Johne's disease by John M'Fadyan and its causative agent, *Mycobacterium avium* subspecies *paratuberculosis (MAP)* was isolated in 1912 by Twort and Ingram and first time named as *chronicae pseudotuberclosis bovis johne* (Goswami *et al.*, 2000; Ayele *et al.,* 2001). Paratuberculosis was reported in subcontinent at 1913 from military farm Lahore (Singh *et al.,* 2010). It is a contagious and chronic disease, lesions are developed in intestine and mesenteric lymph nodes (Cousins *et al.,* 2002). In cattle; *Mycobacterium avium* subspecies *Paratuberculosis* cross the placental barrier and affects the calves. One gram of fecal material of cow at clinical stage of infection consists of more than one million colony forming unit (CFU) of MAP (Naser *et al.,* 2007).

Economic Importance

Paratuberculosis have been considered as a major problem for livestock, zoo and other wild animals (Okuni, 2013) because it causes economic losses like *Trypanosoma evansi* do in horses and donkeys (Bukhari *et al,* 2019), as a result of decrease in milk production (15-16%), low carcass yield, (Moser ,1982; Cousins *et al.,* 2002) decrease weight gain, increase infertility (Singh *et al.,* 2010; Wadhwa *et al.*, 2013), delay parturition (Settles *et al.,* 2011) and premature culling of animals (Arrazuríaa *et al.,* 2014). Annual economic losses in USA exceed up to $1.5 billion. Infection range of Paratuberculosis in dairy herd is variable in different countries like in New Zeeland it is founded to be 12%, USA up to 67% (Zanella *et al.*, 2011), UK 32% (Rhodes *et al.*, 2014), Netherland 54%, Belgium 18%, India 23.3-42.6%, Pakistan 6.67% (Singh *et al.*, 2010), Australia 9-22% and Europe 7-55% (Manning and Collins, 2001).

Etiology and pathogenesis

Mycobacterium is a major group of bacteria that contain more than 50 species, they are rod shaped that may be straight, branched or filamentous, non-spore forming, catalase positive (Kopecna *et al.,* 2008), most of them are non-pathogenic and seem to be related with actinomyces and streptomyces while pathogenic are *M. marinum* (cause swimming pool granuloma), *M. ulcerans* (cause skin disease), *M. laprae* (cause leprosy) and many others, cause infection both in human and animals (Wayne, 1974; Rastogi *et al.*, 2001; Naser *et al.*, 2007). Causative agent of Paratuberculosis is *Mycobacterium johnei* (old name), now a day known as *Mycobacterium avium* subspecies *paratuberclosis* (Greenstein, 2003) is a highly fastidious, aerobic, acid fast, gram positive, non-motile intracellular obligate pathogen in nature (Ayele *et al.,* 2001; Singh *et al.*, 2010; Dow, 2012; Verma, 2013), having good thermal tolerance, resistant to ultraviolet light and can survive in feces, soil and water for a long period (Manning and Collins, 2001) this ability is due to presence of highly thick, hydrophobic and lipid rich cell wall (Rastogi *et al.,* 2001; Ryan, 2006). MAP have two strains that are predictable by using fragment length polymorphism; S strains specific for sheep and C strains specific for cattle, camel, goat and other wild ruminants, both strains have different genome characteristics (Ryan, 2006; *Singh et al.*, 2010).

In adult animals a greater number of MAP are required to cause an infection while young animals are more susceptible. MAP enter into body through

GIT and intracellular multiplication in intestinal mucosa depends upon natural immunity of animal, MAP is taken up through M cells of peyer's patches and then engulfed through macrophages and transferred to the regional lymph node. MAP is resistant against immune system of body and disinfectants. It can survive in acidic and chlorinated water as well as in high temperature environment (Slana *et al.,* 2008; Whittington and Windsor, 2009).

Transmission

MAP comes to an animal herd by purchasing uncertified animal or through carrier animals; it is transmitted through infected environment and through infected calves to other calves. Transmission occurs horizontally via feces and instruments as well as vertically via colostrum of infected mother (Eltholth *et al.,* 2009; Marcé *et al.,* 2011) and intrauterine (Van Kooten *et al.,* 2006; Kopecna *et al.,* 2008). Fecal-oral route is more common in MAP transmission (Stamp and Watt, 1954) while vehicles and equipment's are less common (Arrazuríaa *et al.,* 2014). Crop land grazing also a source of its transmission where infected animal shed MAP with their feces (Bonhotal *et al.,* 2011).

In a herd, MAP spread through vaginal discharge, semen (Singh *et al.,* 2010), embryo transfer technology and also through common watering and feeding with infected animals.

It has long incubation period and can be shed through feces even up to 18 months after appearance of clinical signs. Its transmission depends upon host susceptibility, number of MAP that are ingested and other mechanical or environmental factors (Wadhwa *et al.,* 2013). This issue is controversial for a century that MAP infection is zoonotic due to similarity in signs and symptoms of Paratuberculosis and Crohn's disease (Waddell *et al.,* 2008). It has also been reported that MAP infection is transmitted to human through milk (raw and pasteurized) and milk products (cheese) as well as through meat and meat products.(Mihajlovic *et al.,* 2011; Verma, 2013; Naser *et al.,* 2014).

Clinical findings

Incubation period of MAP is long and signs of infection appear after 2-5 years of onset of disease, MAP infection is categorized into 4 different stages viz are silent infection, unapparent carrier adults, clinical disease and advance clinical disease. First two stages are sub clinical in which chances of other diseases increase such as mastitis and lameness while later two are clinical and are characterized by progressive weight loss, cachexia, watery intermittent diarrhea (Manning and Collins, 2001; Arrazuríaa *et al.,* 2014; Bhattarai *et al.,* 2014), decrease in milk production, less carcass yield (Stamp and Watt, 1954), lymphangitis, lymphadenitis (Moser, 1982), edema due to hypoproteinemia (Sweeney *et al.,* 2012), dehydration, chronic granulomatous inflammation and lesion can be seen in ileum, colon and even in rectum , (Forde *et al.,* 2012). The disease is changed mostly from subclinical to clinical form due to stress, animal become debilitated and emaciated because of absorption of nutrients does not occur through intestine while appetite remains normal till death of animal (Verma, 2013). Animal turn out to be anemic and mucous membranes become pale. It has been reported that wry neck and alopecia could be seen in such animals. According to blood picture of affected animals, leukocytes, granulocytes, liver function enzymes, blood urea nitrogen, creatinine and Mg increase while proteins and hematocrit levels decrease. With the passage of time ileocecal and mesenteric lymph nodes become edematous and inflamed along with development of granulomas on internal organs like liver and spleen (Moser, 1982; Al-Ghamdi, 2013).

Diagnosis

Diagnosis of Paratuberculosis is done by history, clinical signs and symptoms, necropsy findings, direct and indirect laboratory tests. Direct tests include PCR and fecal examination while indirect test is done by ELISA (Cousins *et al.,* 2002), it can also be diagnosed through other group of serological tests such as complement fixation test (CFT) and agar gel immunodiffusion test (AGID). ELISA provide a batter result as compared to others (Ahmed 2010, Wadhwa

et al., 2013) while autopsy and histopathological examination may also be used for confirmation of Paratuberculosis (Laszczych *et al.,* 2010). In an infected animal MAP can not only be isolated from intestinal mucosa or mesenteric lymph nodes but also from lymph nodes of head and mediastinum (Eltholth *et al.,* 2009), it can also be isolated from blood or serum, milk, stool and reproductive tract of infected animal (Arrazuríaa *et al.,* 2014) because MAP spread in extra intestinal parts through lymphatic system and hematogenous route (Whittington and Windsor, 2009). A low sensitivity test; direct fecal sample examination under microscope with Zeil-nelson stain is used to detect acid fast bacilli (Singh *et al.,* 2010) while ELISA is used to detect antibodies that are produced as a result of MAP infection (Masala *et al.,* 2012).

Zoonosis

It has been reported that *Mycobacterium avium* subspecies *Paratuberculosis* also cause infection in human (Hermon-Taylor, 2002) called Crohn's disease is characterized by diarrhea, fever, weight loss, nausea and vomiting (Naser *et al.,* 2014), presence of corrugation and serpiginous ulcers in intestine give "cobble stone" like appearance in humans (Singh and Gopinath, 2011). About 0.5 million of American population is considered as to suffer from Crohn's disease (Stamp and Watt, 1954).

Control

Paratuberculosis is a production limiting disease (O'Brien *et al.,* 2013) and its treatment is not satisfactorily because it is very expensive and impracticable, thus it can be controlled through proper vaccination (Singh *et al.,* 2010, Singh *et al.,* 2014), management and culling of infected animal at proper time. The best way of controlling Paratuberculosis is to minimize or eradicate the present MAP infection and inhibit its re-occurrence in future (Sorge *et al.,* 2010) . Main aim of controlling the MAP infection is to break the fecal-oral or cow-calve cycle of transmission (Whittington and Windsor, 2009). Intake of MAP in food chain should be reduced by abolition of infected animal (Khol and Baunmgartner, 2012). Batter sanitation and isolation play a key role in its controlling (Moser, 1982). After parturition calves should be separated from infected dams (Sweeney *et al.,* 2012) and fed colostrum of non-infected cow through bottle (Nacy and Buckley, 2008; Pieper *et al.,* 2014). Movement of infected cattle should be restricted to a certain area of farm (Geraghty *et al.,* 2014). There should be no compromise on proper hygiene and bio-security. Farmers should have to avoid participating animals in shows because there is a chance of attaining MAP infection from infected animals. Don't use manure of infected animals as fertilizer in fodder crops (Sweeney *et al.,* 2012).Suspected animals should be fed separately. Batter farm hygiene can minimize the chance of MAP infection in herd. Proper waste management and separate milking of suspected animals should be done (Al-Ghamdi, 2013). Avoid overcrowding to minimize the stress of animals (Sohal *et al.,* 2015). We can also control Paratuberculosis through selective breeding by producing such sires and dams that have resistant against MAP (Heuer *et al.,* 2011).

Conclusion

Paratuberculosis is a production limiting disease and characterized by chronic intestinal inflammation, intermittent diarrhea, progressive weight loss and ultimately death of animal.

In a herd; vertical as well as horizontal transmission occurs as a result of fecal contamination, through colostrum or common feeding and watering. It can be diagnosed by clinical examination and through certain biochemical and serological tests such as Polymerase chain reaction, Enzyme linked immunosorbent assay and Ager gel immunodiffusion test. It is considered as non-curable disease and can be controlled by vaccine, proper management and culling of infected animals.

However, further studies are immensely important to know molecular epidemiology and presence of this nightmare in different parts of Pakistan in order to regularize control measures in the infected farms,

detection of possible reservoirs, transmitters and to avoid dissemination of paratuberculosis.

References

Ahmed I. 2010. Serodiagnosis of Johne's disease by indirect ELISA in ovine. Iraqi Journal of Veterinary Sciences **24(1),** 41 (En)-43 (En). (ISSN: 16073894).

Al-Ghamdi G. 2013. Mycobacterium avium subspecies paratuberculosis in camels; Clinical aspects and control suggestions. Egyptian Academic Journal of Biological Sciences **5,** 11-15. http://dx.doi.org/10.21608/EAJBSG.2013.16640

Arrazuríaa R, Arnaiz I, Fouz R, Calvo C, Eires C, Dieguez FJ. 2014. Association between Mycobacterium avium subsp. paratuberculosis infection and culling in dairy cattle herds. Archivos de Medicina Veterinaria **46,** 39-44.

Ayele WY, Machackova M, Pavlik I. 2001. The transmission and impact of paratuberculosis infection in domestic and wild ruminants. Veterinarni Medicina **46(7-8),** 205-224. (Google Scholar indexed, http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.606.4291&rep=rep1&type=pdf

Bhattarai B, Fosgate GT, Osterstock JB, Park SC, Roussel AJ. 2014. Perceptions of veterinarians and producers concerning Johne's disease prevalence and control in US beef cow-calf operations. BMC veterinary research **10(1),** 1. https://doi.org/10.1186/1746-6148-10.27

Bonhotal J, Schwarz M, Stehman SM. 2011. How Mycobacterium avium paratuberculosis is affected by the composting process. Trends in Animal and Veterinary Sciences **2(1),** 5-10. http://dx.doi.org/hdl.handle.net/1813/24404

Cousins D, Condron RJ, Eamens GJ, Whittington RJ, De Lisle GW. 2002. Paratuberculosis (Johne's disease). Australia and New Zealand Standard Diagnostic Procedures **1,** 1-21. https://www.researchgate.net/profile/Richard_Whittington3/publication/228937426_Paratuberculosis_Johnes_Disease/links/548566ad0cf283750c3714afpdf

Dow CT. 2012. M. paratuberculosis heat shock protein 65 and human diseases: bridging infection and autoimmunity. Autoimmune diseases 2012. http://dx.doi.org/10.1155/2012/15082.4

Eltholth M, Marsh VR, Winden SV, Guitian FJ. 2009. Contamination of food products with Mycobacterium avium paratuberculosis: a systematic review. Journal of Applied Microbiology **107(4),** 1061-1071. https://doi.org/10.1111/j.1365-2672.2009.042.86.x

Forde T, Orsel K, Buck JD, Buck SD, Cote SD, Cuyler C, Davison T, Elkin B, Kelly A, Kienzler M, Popko R, Tailon J, Veitch A, Kutz S. 2012. Detection of Mycobacterium avium subspecies paratuberculosis in several herds of Arctic Caribou (Rangifer tarandus ssp.). Journal of wildlife diseases **48(4),** 918-924. https://doi.org/10.7589/2011-09-2.61

Geraghty T, Graham DA, Mullowney P, More SJ. 2014. A review of bovine Johne's disease control activities in 6 endemically infected countries. Preventive veterinary medicine **116(1),** 1-11. https://doi.org/10.1016/j.prevetmed.201406.003

Goswami TK, Joardar SN, Ram GC, Banerjee R, Singh DK. 2000. Association of Mycobacterium paratuberculosis in Crohn's disease and Johne's disease: A possible zoonotic threat. CURRENT SCIENCE-BANGALORE- **79(8),** 1076-1080. https://www.jstor.org/stable/24.104361?seq=1

Greenstein RJ. 2003. Is Crohn's disease caused by a mycobacterium? Comparisons with leprosy, tuberculosis, and Johne's disease. The Lancet infectious diseases **3(8),** 507-514. https://doi.org/10.1016/S1473-3099(03)007.24-2

Hermon TJ. 2002. Treatment with drugs active

against Mycobacterium avium subspecies paratuberculosis can heal Crohn's disease: more evidence for a neglected public health tragedy. Digestive and Liver Disease **34(1),** 9-12. https://doi.org/10.1016/S1590-8658(02)80052-4

Heuer C, Wilson P. Larking K. 2011. Johne's disease in New Zealand livestock. Vetscript **24(2),** 39-41. (Google Scholar indexed, https://www.jdrc.co.nz/s/report-5a1Heuervetscript_Mar11_4-1-2.pdf

Kopecna M, Parmova I, Bartosova LD, Moravkova M, Babak V, Pavlik I. 2008. Distribution and transmission of Mycobacterium avium subspecies paratuberculosis in farmed red deer (Cervus elaphus) studied by faecal culture, serology and IS900 RFLP examinations. Veterinarni Medicina **53(9),** 510-523. (Google Scholar indexed, http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.483.9019&rep=rep1&type=pdf

Laszczych AW, Szteyn J, Ruszczynska A. 2010. A case study of the clinical form of Johne's disease in a heifer. Turkish Journal of Veterinary and Animal Sciences **34(1),** 95-99. https://doi.org/10.3906/vet-0804-8

Manning E. Collins M. 2001. Mycobacterium avium subsp. paratuberculosis: pathogen, pathogenesis and diagnosis. Revue scientifique et technique (International Office of Epizootics) **20(1),** 133-150. Google Scholar indexed. https://pdfs.semanticscholar.org/922d/b3c510803170c4c644d17f9e63ffe09c2574.pdf

Marcé C, Ezanno P, Seegers H, Pfeiffer DU, Fourichon C. 2011. Predicting fadeout versus persistence of paratuberculosis in a dairy cattle herd for management and control purposes: a modelling study. Veterinary Research **42(1),** 36. https://doi.org/10.1186/1297-9716-42-3.6

Masala S, Cossu D, Pacifico A, Molicotti P, Sechi LA. 2012. Sardinian Type 1 diabetes patients, Transthyretin and Mycobacterium avium subspecies paratuberculosis infection. Gut Pathogens **4(1),** https://doi.org/10.1186/1757-4749-4-2.4

Mihajlovic B, Klassen M, Spiringthorpe S, Couture H, Farber J. 2011. Assessment of Sources of Exposure for Mycobacterium avium subsp. paratuberculosis in Food and Wate. International Food Risk Analysis Journal **1(2),** 1-22. (Google Scholar Indexed https://hrcak.srce.hr/file/114175

Moser CL. 1982. Johne's disease (paratuberculosis) in a goat. The Canadian Veterinary Journal **23(2),** 63. (Google Scholar indexed, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1790087/pdf/canvetj00279-0043.pdf

Nacy C, Buckley M. 2008. Mycobacterium avium paratuberculosis: infrequent human pathogen or public health threat. Mycobacterium Avium Paratuberculosis: Infrequent Human Pathogen or Public Health Threat?: 2008; Salem Massachusetts USA: 1-37. Google Scholar indexed, https://www.asmscience.org/content/report/colloquia.colloquia.33?crawler=redirect

Naser SA, Naser NA, Scheld WM, Hooper DV, Hughes JM. 2007. Mycobacterium avium subsp. paratuberculosis and Crohn's disease. Emerging infections **7,** 225-245. (Google Scholar indexed, https://oaktrust.library.tamu.edu/bitstream/handle/1969.1/ETD-TAMU-2510/PEARCE-THESIS.pdf?sequence=1

Naser SA, Sagramsingh SR, Naser AS, Thanigachalam S. 2014. Mycobacterium avium subspecies paratuberculosis causes Crohn's disease in some inflammatory bowel disease patients. World J Gastroenterol **20(23),** 7403-7415. https://doi.org/10.3748/wjg.v20.i23.7403

O'Brien R, Hughes A, Liggett S, Griffin F. 2013. Composite testing for ante-mortem diagnosis of Johne's disease in farmed New Zealand deer:

correlations between bacteriological culture, histopathology, serological reactivity and faecal shedding as determined by quantitative PCR. BMC veterinary research **9(1),** 1. https://doi.org/10.1186/1746-6148-9.72

Okuni JB. 2013. Occurrence of Paratuberculosis in African Countries: a Review. Journal of Veterinary Advances **3(1)**: 1-8. https://scholar.google.com.pk/scholar?hl=en&as_sdt=0%2C5&q=Okuni+JB.+2013.+Occurrence+of+Paratuberculosis+in+African+Countries%3A+a+Review.+Journal+of+Veterinary+Advances+3%281%29%3A+1-8.&btnG.=

Pieper L, Sorge U, Goskin A, DeVries T, Lissemore K, Kelton D. 2014. Management Practices and Their Potential Influence on Johne's disease Transmission on Canadian Organic Dairy Farms—A Conceptual Analysis. Sustainability **6(11),** 8237-8261. https://doi.org/10.3390/su611823.7

Rastogi N, Legrand E, Sola C. 2001. The mycobacteria: an introduction to nomenclature and pathogenesis. Revue Scientifique Et Technique-Office International Des Epizooties **20(1),** 21-54. (Google Scholar Indexed https://www.researchgate.net/profile/Nalin_Rastogi/publication/12044467_The_mycobacteria_an_introduction_to_nomenclature_and_pathogenesis/links/00b7d51c7b997435a9000000.pdf

Rhodes G, Richardson H, Taylor JH, Weightman A, Higham A, Pickup R. 2014. Mycobacterium avium subspecies paratuberculosis: human exposure through environmental and domestic aerosols. Pathogens **3(3),** 577-595. https://doi.org/10.3390/pathogens303057.7

Rodrick J, Herbert J, Richard S. 1984. Ruminant paratuberculosis (Johne's disease): the current status and future prospects. The Cornell Veterinarian **74**: 218-262. (Google Scholar indexed, https://www.researchgate.net/profile/Rodrick_Chiodini/publication/16820257_Ruminant_paratuberculosis_Johne's_disease_The_current_status_and_future_prospects/links/566efcea08ae52dd6c12a5e9/Ruminant-paratuberculosis-Johnes-disease-The-current-status-and-future-prospects.pdf

Ryan T, Campbell D. 2006. Mycobacterium paratuberculosis-a public health issue. New Zealand Food Safety Authority. (Google Scholar Indexed, https://www.researchgate.net/profile/Donald_Campbell7/publication/237324187_Mycobacterium_paratuberculosis_-_A_Public_Health_Issue/links/54f8b15c0cf210398e96c835.pdf

Singh A, Singh SV, Sohal JS. 2010. Is Mycobacterium avium subsp. paratuberculosis, the cause of Johne's disease in animals, a good candidate for Crohn's disease in man? Indian Journal of Gastroenterology **29(2),** 53-58. (Google Scholar indexed, https://www.researchgate.net/profile/Ajay_Vir_Singh/publication/44573758_Is_Mycobacterium_avium_subsp_paratuberculosis_the_cause_of_Johne's_disease_in_animals_a_good_candidate_for_Crohn's_disease_in_man/links/02bfe51396db704bf2000000/Is-Mycobacterium-avium-subsp-paratuberculosis-the-cause-of-Johnes-disease-in-animals-a-good-candidate-for-Crohns-disease-in-man.pdf

Singh S, Gopinath K. 2011. Mycobacterium avium subspecies Paratuberculosis and crohn's regional ileitis: How strong is association? Journal of laboratory physicians **3(2),** 69. https://doi.org/10.4103/0974-272786836

Singh SV, Gupta S, Chaubey KK, Kumar K, Rawat KD, Tiwari R, Dhama K. 2014. Dose standardization studies of Indigenous Vaccine for the control of Mycobacterium avium subspecies Paratuberculosis in naturally infected goats. Advances in Animal and Veterinary Sciences **2,** 17-22. http://dx.doi.org/10.14737/journal.aavs/2014/2.1s.1722

Slana I, Paolicchi F, Janstova B, Navratilova P, Pavlik I. 2008. Detection methods for Mycobacterium avium subsp paratuberculosis in milk and milk products: a review. Veterinarni Medicina-Praha- **53(6),** 283.
https://81.0.228.28/publicFiles/01575.pdf

Sohal J, Singh SV, Singh B, Thakur S, Aseri GK, Jain N, Jayaraman S, Yadav P, Khare N, Gupta S, Chaubey KK, Dhama K. 2015. Control of paratuberculosis: Opinions and practices. Advances in Animal and Veterinary Sciences **3(3),** 156-163.
http://dx.doi.org/10.14737/journal.aavs/2015/3.3.156.163

Sorge U, Kelton D, Lissemore K, Godkin A, Hendrick S, Wells' S. 2010. Attitudes of Canadian dairy farmers toward a voluntary Johne's disease control program. Journal of dairy science **93(4),** 1491-1499.
https://doi.org/10.3168/jds.2009-24.47

Stamp J, Watt J. 1954. Johne's disease in sheep. Journal of Comparative Pathology and Therapeutics **64,** 26-IN26.
https://doi.org/10.1016/S0368-1742(54)800051

Sweeney R, Collins MT, Koets AP, McGuirk SM, Roussel AJ. 2012. Paratuberculosis (Johne's disease) in cattle and other susceptible species. Journal of Veterinary Internal Medicine **26(6),** 1239-1250.
https://doi.org/10.1111/j.1939-1676.2012.01019x

Syed SHB, Muhammad AR, Usman G. 2019. Prevalence of Trypanosoma evansi (Surra) infection in Horses and Donkeys in Attock Region of Punjab, Pakistan. Saudi Journal of Biomedical Research **4(11),** 402-404.
http://dx.doi.org/10.36348/SJBR.2019.v04i11.006

Van Kooten H, Mackintosh CG, Koets AP. 2006. Intra-uterine transmission of paratuberculosis (Johne's disease) in farmed red deer. New Zealand Veterinary Journal **54(1),** 16-20.
https://doi.org/10.1080/00480169.2006.365.98

Verma DK. 2013. Mycobacterium avium subspecies paratuberculosis: an Emerging Animal Pathogen of Global Concern. Advances in Bioresearch **4(4),** 01-08. (Google Scholar Indexed,
http://www.academia.edu/download/41177378/Reviwew_Article_ABR.pdf

Waddell LA, Rajic A, Sargeant J, Harris J, Amezcua R, Downey L, Read S, McEwen SA. 2008. The zoonotic potential of Mycobacterium avium spp. paratuberculosis: a systematic review. Canadian Journal of Public Health/Revue Canadienne de Sante'e Publique: 145-155.
https://doi.org/10.1007/BF03405464

Wadhwa A, Kumar N, Velasco-Villa A, Eda S. 2013. Overview of Johne's disease immunology. Veterinary World **6(11),** 901-904.
http://dx.doi.org/10.14202/vetworld.2013.901-904

Wayne LG. (1974). The Genus Mycobacterium. International Journal of Systematic and Evolutionary Microbiology **24(2),** 308-308.
https://doi.org/10.1099/00207713-24-2-308

Whittington RJ, Windsor PA. 2009. In utero infection of cattle with Mycobacterium avium subsp. paratuberculosis: a critical review and meta-analysis. The Veterinary Journal **179(1),** 60-69.
https://doi.org/10.1016/j.tvjl.2007.08.0.23

Zanella R, Settles ML, McKay SD, Schnabel R, Taylor J, Whitlock RH, Schukken Y, Van Kessel JS, Smith JM, Neibergs HL. 2011. Identification of loci associated with tolerance to Johne's disease in Holstein cattle. Animal Genetics **42(1),** 28-38.
https://doi.org/10.1111/j.1365-2052.2010.020.76.x