Veterinaria

2017 | Volume 4 | Issue 1 | pages 14-20

A Global overview on Bovine Paratuberculosis: A Review

Amjad Khan[a], Muhammad Hassan Mushtaq[b], Mansur Uddin Ahmad[b], Asghar Khan[c] , Muhammad Shakeel[c], Muhammad Ali Shah[d] and Shahid Hussain Farooqi[e]

[a] Faculty of Veterinary Sciences, University of Veterinary and Animal Sciences, Lahore
[b] Department of Epidemiology and public health, Faculty of Veterinary Sciences, University of Veterinary and Animal Sciences, Lahore
[c] Department of clinical studies4, Mehr Ali shah Arid Agriculture University Rawalpindi, Punjab, Pakistan
[d] Department of clinical medicine and surgery, University of Veterinary and animal sciences, Lahore.
[e] Department of Patho-Biology, Pir Mehr Ali shah Arid Agriculture University Rawalpindi, Punjab, Pakistan

Abstract
Johne's disease [Paratuberculosis] is an infectious disease of ruminants, caused by *Mycobacterium avium* subsp. *paratuberculosis* [MAP]. Paratuberculosis is considered to be the most important disease of ruminants. This disease is considerably important because of long incubation period [IP], high economic losses, together with difficulty in diagnosis due to the resemblance with human zoonotic disease, Morbus Crohn's. Animals having latent infection do not show any clinical signs and symptoms but shed high numbers of *Mycobacterium avium* subsp. *paratuberculosis* in excretions and secretions. Economic losses occur as a result low production, infertility, increased susceptibility to other infections, death and culling of diseased animals, respectively. Many studies on the prevalence of MAP have been accomplished throughout the world, but still data of global scenario is missing. Keeping in view the increasing prevalence of MAP, more efforts have to be taken on a supra-regional level to improve the early detection, reduction of Johne's disease and to prevent further spread of this disease in animal species.
Keywords: Bovine; Johne's disease; Diagnosis; Economic importance

Received: 14 June, 2017 **Revised:** 25 August, 2017 **Accepted:** 21 September, 2017
***Corresponding author** Amjad Khan **E-mail:** dramjadkhan77@gmail.com

To Cite This Manuscript: Khan A, Mushtaq MH, Ahmad MU, Khan A, Shakeel M, Shah MA, Farooqi SH. A Global overview on Bovine Paratuberculosis: A Review. Veterinaria 2017; 4(1): 14-21.

Introduction

Paratuberculosis or Johne's disease is infectious chronic granulomatous enteritis of bovines caused by bacterium specie known as Mycobacterium avium subsp. Paratuberculosis, has huge economic loss and a zoonotic potential within dairy herd [1]. In 1895 it was first described by Frothingham and Johne from bovine tuberculosis [2]. Mycobacterium avium paratuberculosis is found all over the world, but the causative pathogen for this disease is more common in wet and temperate environment, while due to zoonotic importance this disease is linked with Human Crohn's disease [3, 4]. Paratuberculosis has been reported from all countries in the world and affect high range of animal species, similarly the disease never occurs in all species in all region of the world but some region or country has very less or no endemic infection[5]. In Tanzania, the disease was first reported in 1960 in two farm which are located in Kilimanjaro state, Although the isolation measure was introduced in 1960 to 1963, but the other cases of these disease has been reported in Morogoro 1994, Arusha 1976 and in Mpwapwa 1984. But the Mbeya region these diseases was last founded in country more than fourteen years ago, in Kitulo dairy farm [6]. The diseased is found worldwide affect the significant economic losses to dairy industry [7, 8]. Once the animals appear clinical signs it becomes resistant to infection leads to chronic diarrhea, cachexia and eventually culling or death of the animal. Initially the pathogens are transmitted through feco-oral route, commonly through ingestion of feed, colostrum, water or milk or other contaminated area [9]. Due to contamination of environment and poor manure management the calves contact with the infected dam is the main source of infection on farm [10, 11]. Recent study shows that the infection transmits through aerosol and inhalation [12]. Vertical transmission is the most common, while the horizontal transmission is through direct contact either from calf to calf or calf to contaminated wildlife [13, 14]. Similarly, the disease is found worldwide but recently it was reported in Pakistan as well 15].

In this article efforts, have been done to review major aspects of bovine paratuberculosis i.e. epidemiology, pathogenesis, clinical profile, diagnostic approaches, economic and zoonotic importance and at the last reviews on some control strategies for this globally alarming disease.

Epidemiology

Some country of the world like Africa the incidence of the disease have been reported but the lacking of data prevalence in some country and are less in others, still there are some parts of the world where it is not endemic [16]. *Mycobacterium avium* subsp. *paratuberculosis* [MAP] affect wide range of ruminants and infected wide range of cattle, sheep, goat and buffaloes [17-19].

Transmission

The transmission of Mycobacterium paratuberculosis through feco-oral route is the most important route; in addition the shedding of pathogen through milk and semen from the diseased animals is also the source of infection. The shedding of pathogens from the infected animals contaminates the water, food and other environmental components. By the ingestion of colostrum and milk from the infected animals the newborn calves are infected but due to the long incubation periods the clinical signs appear in adult life [20-23]. After ingestion, the pathogens are spread through blood and lymph vessels contaminated the internal organs including reproductive organs of male and female [24]. The continuous excretion of MAP in milk, feces and semen of sub-clinical and clinically infected animals increases the environmental load of MAP. The newborn calf get infection from environment or infected dams, in early life but signs developed in later age i.e. 2-6 years in cattle, and the infection enter to fetus by crossing placenta [25]. In calf, horizontal and vertical transmission of disease has been reported [26]. Mycobacterium avium subsp. paratuberculosis is a contagious infection and affected animals shed organism in milk and feces and cattle are infected with age [27-29]. The transmission of infection between the herds is mainly through contaminated food, vehicles, water sources and other equipment. The male animals may carry MAP by infecting water, food and reproductive secretions. The infected Embryo from contaminated and other exposed animals may carry infection and transmit MAP to other clean animals. The calves are usually infected by ingestion of colostrum from another infected cow [64]. It has been reported that calves may shed pathogens in feces at five month of age [27]. Humans can get infection from MAP by using raw meat, milk, and direct contact with carrier animals [31, 32]. Calves may also be infected in early six months of age or in utero. The young animals are more prone, because most probably they have undeveloped cellular immunity. The age relation with MAP infestation has been established in some studies [33].

Pathogenesis

The pathogen enters to the host via feco-oral route, by ingestion of milk, colostrum or contaminated feed. From the infected cattle, the bacilli have been isolated from the reproductive organs and fetuses of the diseased animals. Thus, it is possible to transmit the disease by in-utero. Once the pathogens gain access to the animal's intestine it crosses the ileal mucosal epithelium and enters to the sub epithelial macrophages and persist there. After a prolonged incubation period, the pathogens are continuously shed in the feces and when the animal's age progresses more than two years the clinical signs appear. The most common signs and symptoms in bovines are progressive weight loss, watery diarrhea and marked decreased milk production [34]. In early life of animal, the infection rate is very high but in cattle it does not develop to clinical up to 2-5 years of age [35].

Clinical signs

Paratuberculosis or Johne's disease is chronic granulomatous enteritis in ruminants. Mostly affects cattle, sheep and goats. There is two clinical signs i.e. chronic diarrhea and cachexia but less common in sheep and goats, and have noticeable economic losses in dairy industry [17]. The affected animals have usually good appetite but bubbly and greenish diarrhea is often seen, the animals become cachexic and in some species death is eminent [36]. In dairy cattle, paratuberculosis is categorized into three stages I, II and III. The 1st stage early infection, 2ndstage is subclinical, and 3rdstage is clinical [37]. The 1st stage shows that infections occur butno bacteria shed in the feces. In the 2nd stage, bacteria number increases in intestinal mucosa and intermittent shedding of bacteria takes place in the feces. At 3rd stage, which is the last stage, increase the bacterial load and clinical signs are evident. The affected animal shows clinical signs like weight loss, chronic diarrhea, decreased milk production and anemia [5].

Prevalence

Up till now this disease has been reported in many countries of the world, the herd prevalence in Europe ranges from 7-55% while in USA and Australia it is 40 and 22% respectively [38]. In 1998, in Belgian cattle, 18% herd prevalence was recorded [39]. In 2007 the herd level prevalence of MAP was reported 70.4% in USA after a nine-yeargap. Amongruminants, dairy animals are more susceptible to this disease, but some Australian states and Sweden are proven to be free of this disease [40]. In southern Chile dairy herds the reported herd level prevalence of MAP is 28-100% [41]. A study regarding the sero-prevalence was reported in Arusha which yield an estimateof5.3% [6]. According to a study, in pasteurized milk samples the infection of MAP was reported 1.8% in dairy processing industry [42]. While according to theestimation consensus, there was inadequate information present on the fundamental role of human Crohn's disease[42].In Czech Republic, study reported, 54.7% and 52.5% JD positive animals in dairy herds and beef, individually [44].In South West of England Italy, Belgium, Denmark, Czech Republic, and Netherlands the herd prevalence of JD has been reported 3.5%, 13.3%, 8.0%, 70.0%, 12.0 % and 31-71%, respectively [39,45-47]. In India, the early epidemiological studies were mostly based on Johnin and fecal examination. Limited studies have been recorded in cattle and buffaloes. The prevalence of MAP in Mathura state in dairy was 28.3% from fecal culture and 20.8% by ELISA kit (through indigenous PPA from MAP 'Bison type' of goat origin), respectively [48]. Using milk the diagnostic test, in cattle 96.1% from culture and 88.4% from milk ELISA were positive in Ludhiana. Sero-prevalence in buffalo was recorded to be 21.3% in Chennai, 40.3% in south UP and 25.5% in west UP, respectively [49]. Similarly, using tissue culture from Agra district 48.0% buffalo were positive for MAP infection [50]. Pathologically, it has been recorded that from Bareilly region the MAP infected buffalo were 4.9% [51]. A study have been reported in Haryana, using hypersensitivity reaction that 8.5% of bulls were found positive for MAP using hypersensitivity reaction[52]. The herd prevalence in Slovenia in 1997 was 2.84% but after 11 years the prevalence hasbeen reported 2.77% in2008[53]. The true prevalence among cattle appeared to be approximately 20% andwas at least 3-5% in several countries [53].A study reported from India [south-west Bangalore] that, 15.14% serum positive and 18.33% milk antibody positive has been observed [54].

Similarly, from Pakistan many reports of Paratuberculosis have been given;[56] reported 11.19% [Buffaloes: 12.5%, Cattle: 6.67%] confirmed cases of Johne's disease in 134 suspected samples. It has also been studied in three semen production units in Punjab, Pakistan and confirms cases of Johne's disease were 33% from teaser bulls and 20% from breeding bulls [57]. In report from Pakistan it has been found that in buffalo 12.8% while in cattle 14.2% were found positive for paratuberculosis [19]. Another study compared by two methods; one is tissue section and has high prevalence 100% secondly on smear method which gave only 8.68% [58]. Another comparative study revealed that by acid fast staining in cattle 17.8% MLN and 19.2% intestinal were found positive but in PCR only 14.2% MLN positive while in buffalo by PCR 12.8% and 12.4% were positive for intestinal and MLN, respectively [59]. A recent study on prevalence of bovine paratuberculosis in Pakistan shows it to be 4.1% in cattle and 3.75% in buffaloes [15].

Diagnosis

Due to long incubation periods the diagnosis and detection of Mycobacterium avium subspecies paratuberculosis is difficult and the lack of diagnostic tests which can detect the early infection [60]. On the basis of clinical sign profile, histopathology and postmortem lesion the disease can be diagnosed. The diagnostic tests consist of direct and indirect tests; direct tests include Johnin skin test, fecal culture, PCR and fecal smears while the indirect tests consist of ELISA, agar gel immune-diffusion assay and complement fixation test [61]. It has been reported that the ELISA were the most frequent and considerably a best diagnostic tool for the diagnosis of paratuberculosis[54]. The specificity of two tests was compared; the Johnin skin test and IFN assay showed 93.5% and 93.6% specificity, respectively. The disadvantage of these tests is the lesser specificity while the advantage is their used in the earlier screening [62]. In another it has been reported thatin Danish cattle the milk ELISA has been proven the most preferred and cost effective test than other tests [63].In another study the indirect ELISA was used for the diagnosis of paratuberculosis in South-west Bangalore, [India]in anemic and diarrheic bovines. The sero-prevalence was recorded 15.14% and 18.33% from serum and milk samples, respectively.Further confirmation of the positive cases was carried out by direct smear analysis [55]. Another study used intra dermal Johnin skin test and IFN gama for the diagnosis of Johne's disease and gave significant results[64].On

2017 | Volume 4 | Issue 1 | pages 14-20

the basis of real time PCR [rtPCR] 28.6% bulk tank milk were positive for Mycobacterium paratuberculosis in dairy cattle in Cyprus [22]. In Pakistan, a study reported that the diagnosis of johne's disease can be successfully carried out using histopathology, ELISA, acid fast staining and PCR [58, 19]. The differential diagnosis *M. paratuberculosis* consists of chronic infectious diseases, gastrointestinal parasitism, peritonitis, kidney failure, copper deficiency, renal amyloidosis and chronic salmonellosis [51].

Economic and zoonotic importance

Paratuberculosis is an important disease of dairy animals that cause a significant losses to dairy industry all over the world and is now the most dominant and costly disease of dairy cattle, the most important losses from Mycobacterium avium paratuberculosis includes; milk production fall, increase the incidence of mastitis, poor body condition scores and also effect on the reproductive status of the animals i.e. infertility also increase the indirect losses due to premature culling, death of the animals and diagnostic tests. The disease can cause huge economic losses to dairy farmers due to the loss of milk production and culling of diseased animals [65]. Annual losses due to Johne's disease to US dairy are estimated to be between 200 and 250 million US$. Johne's disease causes significantly, high economic losses in developed and developing countries**.** In the sub-clinical stage of infection most of the losses occurs in the form of progressive weight loss, lower slaughter value, decreased milk production, reduced fertility, and premature culling. Economiclosses due to paratuberculosis have been reported, US- $200-250million, New England - $15.4 million, Australia- $2.1million, Wisconsin -$52.3 million, Pennsylvania $5.4 million [11]. The annual losses on treatment and direct production were estimated on an average 7% in JD infected cow herd andfound that the huge losses occur due to; paratuberculosis [USD 2 472] than neosporosis, bovine viral diarrhea, and enzooticbovine leukosis, respectively[66]. Although the majority of [185.5 million] Indian cattle are unproductive or low productive, but still have never been screened for JD. Mycobacterium avium subsp. paratuberculosis [MAP] has emerged as major successful pathogen of animal with significantzoonotic potential and public health concern [43]. In different animal species, the pathology of disease differs in different tissues within animals. The affected animals are unable to absorb fluid and digested nutrients from intestinal tract. These animals, if do not recover, may die, but the appetite may remain normal till death. The diagnostic measures available for JD suffers with poor specificity and sensitivity and in early stage of disease do not detect the infection. The culture has been considered as a 'Gold standard' test to date but it has limitations. At postmortem, the most confirm diagnoses are made after death. There is no treatment of paratuberculosis, because different antimicrobials drugs have been tried for treatment of JD but none proved a long-term option due to more cost associated with treating whole herd for prolong period[68].

Mycobacterium avium paratuberculosis has been concerns with human Crohn's disease as well as

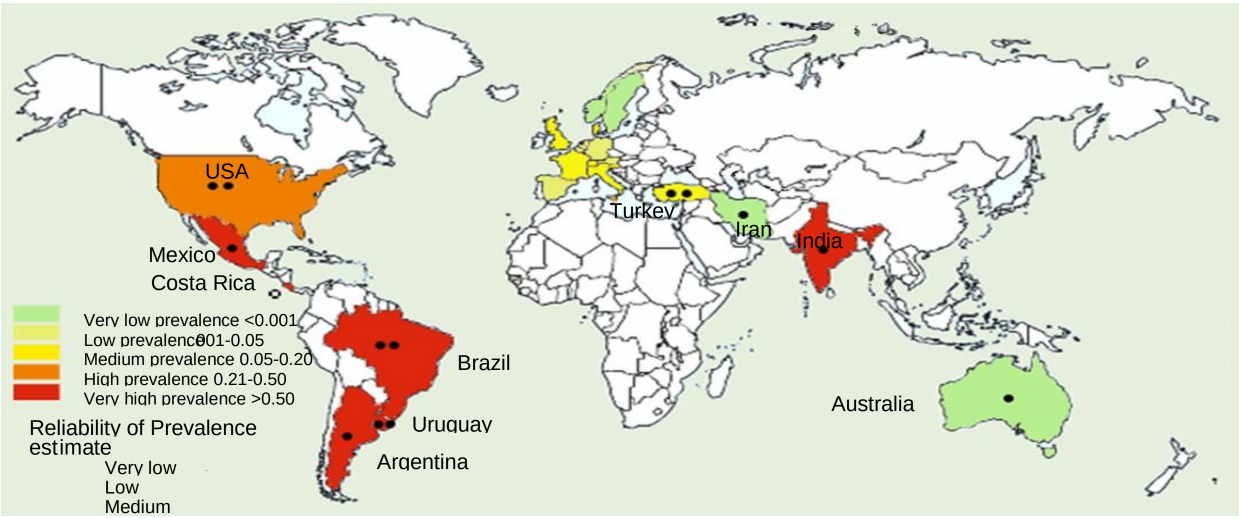

Fig: 1. Prevalence of individual animal of infected paratuberculosis dairy cattle in the world courtesy of [75].

2017 | Volume 4 | Issue 1 | pages 14-20

sarcoidosis. Currently, MAP has been related to Blau syndrome [juvenile sarcoidosis], autoimmune thyroiditis, autoimmune diabetes and multiple sclerosis. While the MAP is associated with granulomatous disease where the microbe joins in the granuloma, it is difficult to give the role for MAP in diseases where the autoantibodies are main feature because the MAP may activate the autoimmune antibodies through heat shock proteins [69].

Control and prevention

The presence of an identified animal infection, with a zoonotic potential, unpasteurized milk samples, should follow discard of the dairy product and legislative approaches to deal the problem. In future, a comprehensive information regarding, seroprevalance of MAP, epidemiological designs and incidence in cattle is of great worth to facilitate the strategy of prevention and control policy. The transmission of MAP is a key section of control programs with the purpose to reduce or eliminate the MAP infection from farms [70]. Vaccination of animals is one of the control measure for Johne's disease, is possibly the less accepted strategy while has been used in all countries with considerable problems of this disease [71]. If the vaccination has been done carefully that will prevents the appearance of clinical cases because it is a highly cost-efficient policy [72]. The only disadvantage of vaccination is that, vaccines are used in the field that hampers the sero diagnosis by difficulty in differentiating infected from vaccinated [DIVA], it can affect with serological diagnosis of Johne's disease. It means that MAP vaccinations not allow eradication of the disease but it can interfere with national tuberculosis eradication strategies. The medical and agriculture authorities for the approval of major herd affecting MAP vaccine all over the world and some new MAP vaccines for dairy cattle as a major preventive tool by the pharmaceutical companies are designed. The single intradermal tuberculin test is the most commonly used diagnostic test for tuberculosis and there are chances that some cattle vaccinated against the currently available ovine or experimental mycobacterium paratuberculosis vaccines will be positive to the tuberculin test. According to legislation Johne's disease positive animals are banned from international trade and are slaughtered. The Enferplex^{TM} a new tuberculosis immunological diagnostic test may help to differentiate between MAP tuberculosis infected and vaccinated animals, but the developments of test might be necessary, the diagnosis of tuberculosis interference with Mycobacterium paratuberculosis infected animals [73].

In a majority of cases variation of a single tuberculin intradermal test can solve the interference problems. According to the EU and OIE legislation the available test for many years is actually an official tuberculin test and it consists of immediate intradermal injection in two different locations of tuberculin's from Mycobacterium avium subsp. avium and Mycobacterium bovis. The avian tuberculin shows the high reactivity of vaccination or infection with avia type mycobacterium and allows the infection of mammal tuberculosis to be ruled out, according to uniform criteria. At the last, there are some approaches for paratuberculosis control, but still there is no widespread agreement on which one or combination of methods would be the standard approach. In our opinion the Johne's disease control policy could eradicate the MAP stress successfully [74].The ranking of JD with respect to national prevalence in poor and underdeveloped countries, the production losses, diagnosis, control measures, and the prevalence in other animals is unknown. The information regarding prevalence of JD in India is incomplete due to huge ruminant population about 500 million ruminants [68].

Conclusions

Farmer and veterinarian are facing challenges in controlling the Paratuberculosis. Test and culling policies could be helpful in some locations but do not appear to reached the desired success. An alternative control by vaccination can prove to be along-time policy in some areas. Rising incidences of Johne's disease, presence of MAP in food chain are alarming signs for public health. Due to high economic losses, long incubation period, difficult diagnosis, strong survival potential, existence in human food chain and possible link to CD, MAP as an emerging pathogen of global concern. Here is an urgent need of designing some strategy for the successful control on spread of MAP in animals and preventing its transmission to human from animals, animal's byproducts, nationally and internationally.

References

[1] Arsenault RJ, Maattanen P, Daigle J, Potter A, Griebel P, Napper S. From mouth to macrophage: mechanisms of innate immune subversion by Mycobacterium avium subsp. paratuberculosis. Vet Res 2014; 45(1):54.

[2] Johne H, Frothingham L. Ein eigenthuemlicher fall von tuberculose beim rind. Dtsch. Z. Tiermed. Pathol 1895; 21:438-454.

[3] Benedictus G, Dijkhuizen A, Stelwagen J. Economic losses due to paratuberculosis in dairy cattle. Vet Rec 1987; 121(7):142-146.

[4] Hutchinson LJ. Economic impact of paratuberculosis. The Veterinary clinics of North America. Food animal practice1996; 12 (2):373-381.

[5] Vansnick E. Johne's disease in zoo animals: development of molecular tools for the detection and characterisation of Mycobacterium avium subspecies paratuberculosis. PhD study, RUGhent 2004; 10.

[6] Vansnick E. Johne's disease in zoo animals: development of molecular tools for the detection and characterisation of Mycobacterium avium subspecies paratuberculosis. PhD study, RUGhent 2004; 10.

[7] Barkema HW, Hesselink JW, McKenna SL, Benedictus G, Groenendaal H. Global prevalence and economics of infection with Mycobacterium avium subsp. paratuberculosis in ruminants. Paratuberculosis: Organism, Disease, Control. Ed: Marcel A. Behr and Demond M. Collins. CABI, United Kingdom 2010; 10-21.

[8] Wolf R, Clement F, Barkema H, Orsel K. Economic evaluation of participation in a voluntary Johne's disease prevention and control program from a farmer's perspective-The Alberta Johne's Disease Initiative. J dairy sci 2014; 97(5):2822-2834.

[9] Tiwari A, VanLeeuwen JA, McKenna SL, Keefe GP, Barkema HW. Johne's disease in Canada Part 1: Clinical symptoms, pathophysiology, diagnosis, and prevalence in dairy herds. Canadian Vet J 2006; 47(9):874.

[10] Johnson-Ifearulundu YJ, Kaneene JB. Management-related risk factors for M. paratuberculosis infection in Michigan, USA, dairy herds. Preventive Vet Med 1998; 37(1): 41-54.

[11] Wells SJ, Wagner BA. Herd-level risk factors for infection with Mycobacterium paratuberculosis in US dairies and association between familiarity of the herd manager with the disease or prior diagnosis of the disease in that herd and use of preventive measures. J American Vet Med Associ 2000; 216(9):1450-1457.

[12] Eisenberg S, Nielen M, Santema W, Houwers D, Heederik D, Koets A. Detection of spatial and temporal spread of Mycobacterium avium subsp. paratuberculosis in the environment of a cattle farm through bio-aerosols. Vet Microbiol 2010; 143(2):284-292.

[13] Sweeney RW. Transmission of paratuberculosis. The Veterinary clinics of North America. Food ani pract1996; 12(2):305-312.

[14] Fischer O, Matlova L, Dvorska L, Svastova P, Peral D, Weston R, Bartos M, Pavlik I. Beetles as possible vectors of infections caused by Mycobacterium avium species. Vet Microbiol 2004; 102(3):247-255.

[15] Waqas A, Javed M. K. Ashfaque, Mehwish Q. An Abat-toir Based Study on Brucellosis, Bovine Tuberculosis and Paratubercu-losis in Buffaloes and Cattle at Faisalabad, Pakistan. Int J Vet Health Sci Res 2015; 3 [1]: 34-38.

[16] Okuni JB. Occurence of Paratuberculosis in African Countries: a Review. J. Vet. Adv 2013; 3 [1]: 1-8.

[17 Rosseels V, Huygen K. Vaccination against paratuberculosis. Expert Rev Vaccines 2008; 7(6):817-832.

[18] Singh SV, Chaubey KK, Gupta S, Gupta VK, Agrawal ND, Kumar N.
Co-infection of Mycobacterium aviumsubspecies paratuberculosis and
Brucellamelitensisin a sirohi breed of goats in India. Adv. Anim. Vet. Sci 2013; 1(6):188 - 190.

[19] Khan FA, Chaudhry ZI, Ali MI, Khan S, Mumtaz N, Ahmad I. Detection of Mycobacterium avium subsp. paratuberculosis in tissue samples of cattle and buffaloes. Trop ani healthprod 2010; 42(4):633-638.

[20] Giese SB, Ahrens P. Detection of Mycobacterium avium subsp. paratuberculosis in milk from clinically affected cows by PCR and culture. Vet Microbiol 2000; 77(3):291-297.

[21] Slana I, Kralik P, Kralova A, Pavlik I. On-farm spread of Mycobacterium avium subsp. paratuberculosis in raw milk studied by IS900 and F57 competitive real time quantitative PCR and culture examination. Int J food Microbiol 2008; 128(2):250-257.

[22] Slana I, Liapi M, Moravkova M, Kralova A, Pavlik I. Mycobacterium avium subsp. paratuberculosis in cow bulk tank milk in Cyprus detected by culture and quantitative IS900 and F57 real-time PCR. Prev Vet Med 2009; 89(3):223-226.

[23] Kurade N, Tripathi B, Rajukumar K, Parihar N. Sequential development of histologic lesions and their relationship with bacterial isolation, fecal shedding, and immune responses during progressive stages of experimental infection of lambs with Mycobacterium avium subsp. paratuberculosis. Vet Pathol2004; 41(4):378-387.

[24] Ayele WY, Machackova M, Pavlik I. The transmission and impact of paratuberculosis infection in domestic and wild ruminants. Vet Med 2001; 46(7-8):205-224.

[25] Buergelt C, Donovan G, Williams J. Identification of Mycobacterium avium subspecies paratuberculosis by polymerase chain reaction in blood and semen of a bull with clinical paratuberculosis. Intern J Appl Res Vet Med2004; 2(2):130-134.

[26] Van Roermund H, Bakker D, Willemsen P, De Jong M. Horizontal transmission of Mycobacterium avium subsp. paratuberculosis in cattle in an experimental setting: calves can transmit the infection to other calves. Vet microbiol 2007; 122(3):270-279.

[27] Hasonova L, Trcka I, Babak V, Rozsypalova Z, Pribylova R, Pavlik I. Distribution of

[28] Mycobacterium avium subsp. Paratuberculosis in tissues of naturally infected cattle as affected by age. Vet Med 2009; 54(6):257-269.

[29] Hines ME II, Stabel JR, Sweeney RW, Griffin F, Talaat AM, Bakker D, Benedictus G, Davis WC, de Lisle GW, Gardner IA, Juste RA, Kapur V, Koets A, McNair J, Pruitt G, Whitlock RH. Experimental challenge models for Johne's disease: A review andproposed international guidelines. Vet Microbiol 2007;122:197-222

[31] Seyyedin M, Zahraei T, Najafi MF. Comparison of isolation frequency of Mycobacterium avium subspecies Paratuberculosis from different types of samples. Pak. Vet. J 2010; 30(3):143-149.

[32] Stabel JR. Pasteurization of colostrum reduces the incidence of Paratuberculosis in neonatal dairy calves. J Dairy Sci 2008; 91(9):3600-6.

[33] Eltholth MM, Marsh VR, Van Winden S, Guitian FJ. Contamination of food products with Mycobacterium avium paratuberculosis: a systematic review. J Appl Microbiol 2009; 107(4):1061-1071

[34] Alluwaimi AM. The etiology of Mycobacterium avium subspecies Paratuberculosis in Crohn'sdisease. Saudi Med J 2007; 28(10):1479-1484.

[35] Windsor PA, Whittington RJ. Evidence for age susceptibility of cattle to Johne's disease. Vet J 2010; 184(1):37-44.

[36] Clarke C. The pathology and pathogenesis of paratuberculosis in ruminants and other species. J Comp Pathol1997; 116(3):217-261.

[37] Maxie MG, KVF Jubb, PC Kennedy and NC Palmer.Pathol Domestic Ani 2007; 5th Ed. Vol. 2. Saunders Elsevier, London, pp: 222-225.

[38] Gwozdz JM. Paratuberculosis [Johne's disease]. Australian and New Zealand Standard 2010;

[39] Wadhwa A, Kumar N, Velasco-Villa A, Eda S. Overview of Johne's disease. Immunology. Vet World 2013; 6(11):901-904.

[40] Manning E, Collins M. Mycobacterium avium subsp. paratuberculosis: pathogen, pathogenesis and diagnosis.

Revue scientifique et technique [International Office of Epizootics] 2001; 20(1):133-150.
[41] Boelaert F, Walravens K, Biront P, Vermeersch J, Berkvens D, Godfroid J. Prevalence of paratuberculosis [Johne's disease] in the Belgian cattle population. Vet Microbiol 2000; 77(3):269-281.
[42] Lombard JE, Gardner IA, Jafarzadeh SR, Fossler CP, Harris B, Capsel RT, Wagner BA, Johnson WO. 2013. Herd-level prevalence of Mycobacterium avium subsp. paratuberculosis infection in United States dairy herds in . Prev Vet Med 2007; 108(2-3):234-238.
[43] Kruze J, Monti G, Schulze F, Mella A, Leiva S. Herd-level prevalence of Map infection in dairy herds of southern Chile determined by culture of environmental fecal samples and bulk-tank milk qPCR.Prev. Vet. Med 2013; 111(3-4):319-24
[44] Grant IR, Ball HJ, Rowe MT. Incidence of Mycobacterium paratuberculosis in bulk raw and commercially pasteurized cows' milk from approved dairy processing establishments in the United Kingdom. Appl Env Microbiol 2002; 68 (5):2428-2435.
[45] Grant I. Zoonotic potential of Mycobacterium avium ssp. paratuberculosis: the current position. J Appl Microbiol 2005; 98(6):1282-1293.
[46] Ayele WY, Svastova P, Roubal P, Bartos M, Pavlik I. Mycobacterium avium subspecies paratuberculosis cultured from locally and commercially pasteurized cow's milk in the Czech Republic. Appl Env Microbiol 2005; 71(3):1210-1214.
[47] Jakobsen MB, Alban L, Nielsen SS. A cross-sectional study of paratuberculosis in 1155 Danish dairy cows. Prev Vet Med 2000; 46(1):15-27.
[48] Muskens J, Barkema HW, Russchen E, van Maanen K, Schukken YH, Bakker D. Prevalence and regional distribution of paratuberculosis in dairy herds in The Netherlands. Vet Microbiol 2000; 77(3-4):253-261.
[49] Kennedy DJ, Benedictus G. Control of Mycobacterium avium subsp. paratuberculosis infection in agricultural species. Rev Sci Tech 2001; 20(1):151-179.
[50] Mishra, P.K., Singh, S.V., Bhatia, A.K., Singh, P.K., Singh, A.V., Kulshreshtha, C.M., Sohal, J.S. In: National seminar on Emerging diseases of small ruminants and there containment under WTO regie 2007; pp 21-22.
[51] Singh SV, Singh AV, Singh R, Sharma S, Shukla N, Misra S, Singh PK, Sohal JS, Kumar H, Patil PK, Misra P, Sandhu KS. Sero-prevalence of bovine Johne's disease in buffaloes and cattle population of North India using indigenous ELISA kit based on native Mycobacterium avium subspecies paratuberculosis 'Bison type' genotype of goat origin. Comp Immunol Microbiol Infect Dis2008; 31(5):419-433.
[52] Sivakumar P, Tripathi B, Singh N. Detection of Mycobacterium avium subsp. paratuberculosis in intestinal and lymph node tissues of water buffaloes [Bubalus bubalis] by PCR and bacterial culture. Vet Microbiol 2005; 108(3):263-270.
[53] Yadav D, Singh S, Singh A, Sevilla I, Juste R, Singh P, Sohal J. Pathogenic 'Bison-type'Mycobacterium avium subspecies paratuberculosis genotype characterized from riverine buffalo [Bubalus bubalis] in North India. Comp Immunol Microbiol infect dis 2008; 31(4):373-387.
[54] Raut A, Manju A, Kumar B, Sethi R. Prevalence of paratuberculosis in breeding buffalo bulls at organized farms. In: Proceedings of the fourth Asian Buffalo Congress on Buffalo for Food Security and Rural Employment 2003; 18.
[55] Ocepek M, Pogačnik M, Logar K, Ferme D, Pate M, Krt B, Nielsen S. Seroprevalence of paratuberculosis in cattle in Slovenia. In: Proceedings of the 10th International Colloquium on Paratuberculosis, Minneapolis, Minnesota, USA, 9-14 August 2009: Int Associ Paratuber 2009; 73-75.
[56] Nielsen SS, Toft N. Ante mortem diagnosis of paratuberculosis: a review of accuracies of ELISA, interferon-γ assay and faecal culture techniques. Vet Microbiol 2008 129(3):217-235.
[57] Gupta A, Rani SM, Agrawal P, Gupta PK. Sero-prevalence of paratuberculosis [Johne's Disease] in cattle population of South-Western Bangalore using ELISA kit 2012;
[58] Sikandar A, Cheema AH, Younus M, Aslam A, Zaman MA, Rehman T. Histopathological and serological studies on paratuberculosis in cattle and buffalos. Intern Workshop on Dairy Sci Park 2011; Peshawar, Pakistan. 21-23/11/2011.
[59] Abbas M, Munir M, Khaliq SA, Ikram Ul Haq M, Khan MT, Qureshi ZA. Detection of Paratuberculosis in Breeding Bulls at Pakistani Semen Production Units: A continuous Source of Threat. ISRN Vet Sci 2011;vol. Article ID 501235.
[60] Sikandar A, Adil M, Ansari AR, Nasir A, Rehman TU. Histological evaluation of the gut of nili-ravi buffaloes for diagnosing paratuberculosis. Buffalo Bulletin 2007; 2014; 33:4.
[61] Chaudhry ZI, Khan FA, Badar S, Shahid M. Detection of Mycobacterium avium subsp. paratuberculosis in domestic ruminants in Lahore, Pakistan. Pakistan J Zool 2009; 41(2):160-163.
[62] Nielsen SS, Jepsen OR, Aagaard, K. Control programme for paratuberculosis in Denmark. Bull. Int. Dairy Federat 2007; 410:23-29.
[63] Munir MT, Munir AR, ul Hasan M, Abubakar M. 2014. Epidemiology and Management Strategies of Johne's disease in Endemic Situations.
[64] Kalis C, Collins M, Hesselink J, Barkema H. Specificity of two tests for the early diagnosis of bovine paratuberculosis based on cell-mediated immunity: the Johnin skin test and the gamma interferon assay. Vet Microbiol 2003; 97(1):73-86.
[65] Sergeant E, Nielsen SS, Toft N. Evaluation of test-strategies for estimating probability of low prevalence of paratuberculosis in Danish dairy herds. Prev Vet Med 2008; 85(1):92-106.
[66] Stabel JR, Kimura K, Robbe-Austerman S. Augmentation of secreted and intracellular gamma interferon following johnin purified protein derivative sensitization of cows naturally infected with Mycobacterium avium subsp. paratuberculosis. J Vet Diag Inv 2007; 19(1):43-51.
[67] Hasonova L, Pavlik I. Economic impact of paratuberculosis in dairy cattle herds: a review. Vet Med 2006; 51(5):193-211.
[68] Chi J, VanLeeuwen JA, Weersink A, Keefe GP. Direct production losses and treatment costs from bovine viral diarrhoea virus, bovine leukosis virus, Mycobacterium avium subspecies paratuberculosis, and Neospora caninum. Prev Vet Med 2002; 55(2):137-153.
[69] Sockett DC. Johne's disease eradication and control: regulatory implications. The Veterinary Clinics of North America. Food Ani Pract 1996; 12(2):431-440.
[70] Verma DK. Mycobacterium avium subspecies paratuberculosis: an Emerging Animal Pathogen of Global Concern. Advances in Bioresearch 2013; 4(4).
[71] Dow CT. M. paratuberculosis Heat Shock Protein 65 and Human Diseases: Bridging Infection and Autoimmunity. Autoimmune Dis2012; 150824.
[72] Woodbine KA, Schukken YH, Green LE, Ramirez-Villaescusa A, Mason S, Moore SJ, Bilbao C, Swann N, Medley GF. Seroprevalence and epidemiological characteristics of Mycobacterium avium subsp. paratuberculosis on 114 cattle farms in south west England. Prev Vet Med 2009; 89 [1]: 102-109.
[73] Saxegaard F, Fodstad F. Control of paratuberculosis [Johne's disease] in goats by vaccination. Vet Rec1985; 116(16):439-441.
[74] Fridriksdottir V, Gunnarsson E, Sigurdarson S, Gudmundsdottir K. Paratuberculosis in Iceland: epidemiology and control measures, past and present. Veterinary microbiology 2000 ; 77(3):263-267.
[75] Barry C, Corbett D, Bakker D, Andersen P, McNair J, Strain S. The effect of Mycobacterium avium complex infections on routine Mycobacterium bovis diagnostic tests. Vet Med Int 2011;
[76] Bastida F, Juste RA. Paratuberculosis control: a review with a focus on vaccination. J Immune Based Ther Vaccines2011; 9 8.
[77] Guicharnaud M. Prevalence of paratuberculosis in dairy cattle herd worldwide: review and analysis[in French], Doctorate in Veterinary Medicine Thesis, Nantes, 2009.