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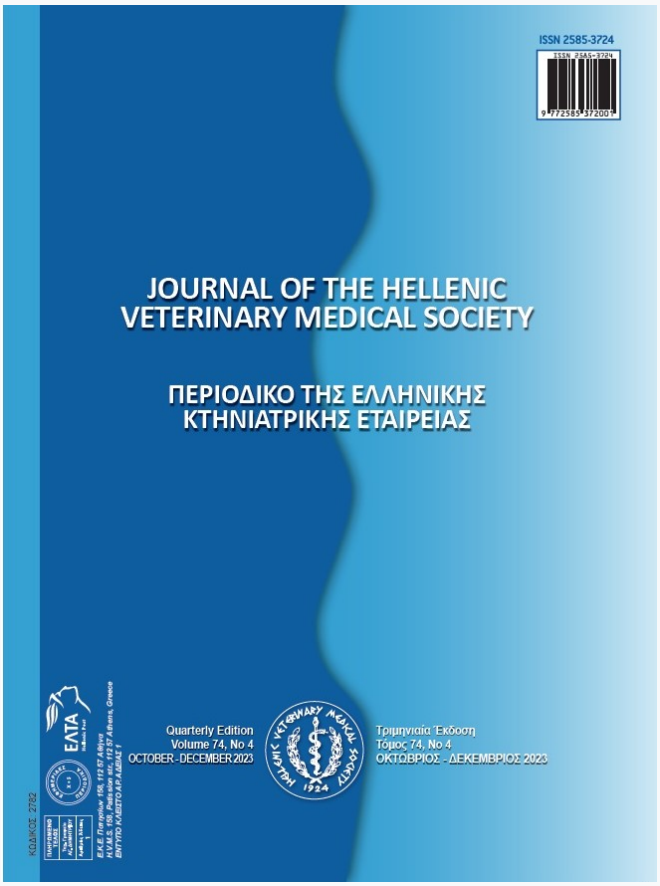

Toward paratuberculosis control in animals: current updates and future perspectives

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Review article
Ανασκόπηση

Toward paratuberculosis control in animals: current updates and future perspectives

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ABSTRACT: Paratuberculosis is a chronic non-curable disease that affects domesticated and wild ruminants, pets, and even humans. Many countries have implemented control programs to eradicate the disease. Such programs face great challenges due to the nature of the pathogen itself, the immune response, the method of pathogen shedding in susceptible animals, and the absence of accurate diagnostic tools, efficient vaccines, and curative medication. However, some control programs succeeded in disease eradication, others achieved less success. The present review discusses the elements required in disease control protocols and highlights the importance of disease elimination. These control strategies include the optimum application of management measures and the proper use of combined diagnostic techniques to accurately identify MAP-infected animals with high sensitivity and specificity. Nanotechnology has shown promising results in the diagnosis and control of paratuberculosis. Available vaccines reduce clinical signs, pathogen shedding, and provoke cellular and humoral immune responses. Although the test and slaughter policy of paratuberculosis is considered an effective way for its control, several obstacles hinder its application.

***Keywords*:** Paratuberculosis; Crohn`s disease, Nano-immunotest; Stem cell therapy; Fecal transplantation.

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INTRODUCTION

Paratuberculosis (Johne's disease, JD) is a chronic inflammatory disease that affects mainly ruminants. JD is caused by *Mycobacterium avium* subsp. *paratuberculosis* (MAP), a member of the *Mycobacterium avium* complex (MAC) (Fawzy et al., 2013). The disease is responsible for huge economic losses in the dairy industry. The subclinical form of JD is the most common form, therefore,asymptomatic shedders remain unnoticed (More et al., 2015, Salem et al., 2005). The consumption of contaminated milk from such cows results in human infections. MAP is accused of being one of the causative agents of Crohn's disease (CD), chronic enteritis, inflammatory bowel disease (IBD), and Sjogren's syndrome (SS) (Dow and Chan 2021, Honap et al., 2020b, Okuni et al., 2020). MAP exhibits clear molecular mimicry with human antigens. Therefore, infection with MAP results in serious autoimmune diseases, including multiple sclerosis, Hashimoto's thyroiditis, and type 1 diabetes mellitus (Chaubey et al., 2020, Garg et al., 2020a).

Recently published data continue to implicate MAP as the inducer of CD and Sjogren's syndrome (SS) (Agrawal et al., 2020b). Whether human paratuberculosis is correlated with CD or not remains controversial (Waddell et al., 2016, McNees et al., 2015, Waddell et al., 2015, El-Sayed et al., 2013b). SS syndrome affects the exocrine glands and manifests as polyarthritis, polyarthralgia, polymyalgia, bronchiectasis, and organ vasculitis, in addition to lung clinical signs. Similar to CD, predisposing genetic factors and environmental triggers are required to develop Sjogren's syndrome (Dow and Chan 2021).

MAP is a very robust pathogen.Pasteurization and UV treatment of the milk are not efficient in killing MAP. Viable bacteria were detected in infant milk powder (McAloon et al., 2019, Botsaris et al., 2016, Fawzy et al., 2016, HRUSKA et al., 2012, Bastida and Juste 2011, Donaghy et al., 2009). MAP also survives unfavourable environmental conditions, composting, manure packing, and even liquid storage of farm manure for several months. The pathogen also persists in soil, crops, and ensiled feed. However, it is less resistant to hot and dry weather (Manning and Collins 2001, Whittington et al., 2004, Grewal et al., 2006, Fecteau et al., 2013).

The prevalence of paratuberculosis varies significantly according to the success of control programs, hygienic measures, and vaccination strategies. However, the prevalence was roughly estimated to be about (53%) in Africa, 20% (Europe), 16.9% (North America), 18.3% (South America), 6.8% (Australia), and 23.3% in India (Agrawal et al., 2021). The reported numbers in the literature may vary according to the used screening assay (allergic test, culture, serological screening, or polymerase chain reaction (PCR)), the reporting year, the animal species (dairy cattle, beef, sheep, goat, camels, farmed deer, or wild animals), and age group, and whether the data describe the individual animal or the herd prevalence (Whittington et al., 2019). The prevalence of MAP in different countries is listed in Table 1.

Table 1 The table lists the prevalence of MAP in different countries and the used assay for the screening purposes.

Country	Prevalence	Method	Reference
USA	Dairy cattle herds 76.92%	PCR	(Toth et al., 2011)
Mexico	Dairy cattle herds 5%	ELISA	(Mili et al., 2015)
Mexico	Sheep at flock level 53.5%	ELISA	(Morales-Pablos et al., 2020)
Colombia	MAP prevalence is 8% of indiv. animals and 70.8% of the flocks	ELISA	(Hernández-Agudelo et al., 2021)
South America	On the cattle herd-level: 35.3 % (Brazil), 35.3 % (Chile), 11.8 % (Venezuela), 5.9 % (Mexico), 5.9 % (Puerto Rico), and 5.9 % (Costa Rica).	ELISA	(Fernández-Silva et al., 2014)
Brazil	The cattle herd-level prevalence in Paraíba (34.5%), in Borborema (26.6%), Agreste/Mata (30.5%), and Sertão (41.4%)	ELISA	(Vilar et al., 2015)
Ecuador	Dairy cattle 25% of the tested animals	ELISA	(Echeverría et al., 2014)
Pakistan	2.4% at the individual animal level and 100% at cattle farm/herd-level	ELISA	(Hussain et al., 2018)

Pakistan	The prevalence at animal level in dairy buffaloes is 1.3%	ELISA	(Rehman 2017)
India	Dairy cattle (15%)	ELISA	(Gupta et al., 2012)
India (West Bengal)	Dairy cattle (37.7%)	ELISA	(Bhutediya et al., 2017)
Egypt	in dairy cattle farms in Ismailia governorate (66%), Monofia (54%), in Fayoum, Sharkeya (29%), Mansoura (25%) and Gharbia (5%).	ELISA	(Fawzy et al., 2013)
Egypt	Ovine paratuberculosis ranged between 3.75%-12.3% in different governorates	ELISA	(Selim et al., 2021)
Sudan (Khartoum State)	MAP prevalence at the animal and herd levels is 6.3% and 18.9%, respectively.	ELISA	(Elmagzoub et al., 2020)
Algeria	The prevalence ranges from 8 % (by ELISA) to 54 % (by histopathological examination).	ELISA	(Hemida and Kihal 2015)
New Zealand	Beef (42%)	PCR	(Verdugo et al., 2014)
Australia	Ovine paratuberculosis in 5% of the national sheep flock	ELISA	(Windsor 2015)
Switzerland	Dairy (83.3%) Beef (72.7%)	ELISA	(Keller et al., 2014)
Belgian	The true herd prevalence for dairy, mixed, and beef herds was, respectively, 10, 11, and 3%.	ELISA	(Boelaert 2000)
Lombardy and Veneto regions (Italy)	70% of the dairy farms.	ELISA	(Pozzato et al., 2011)
Hungary	89.1 % of Hungarian dairy cow herd-level true prevalence	ELISA	(Ozsvari et al., 2020)
Spain	Dairy (4.03%), Beef (2.07%), Mixed (3.84%)	ELISA	(Diéguez et al., 2007)
Irland	Dairy (2.74%) and beef (3.09 %)	ELISA	(Good et al., 2009)
Germany	Dairy (6.7%)	ELISA	(Denzin et al., 2011)

ECONOMIC IMPORTANCE OF PARATUBERCULOSIS

MAP control programs have been implemented, resulting in disease eradication in several countries,as Sweden and Norway (Whittington et al., 2019). The disease induces huge direct and indirect economic losses,including premature culling, reduction in body weight and milk production, and decreased herd immunity, in addition tothe costs of testing, medication, and trade restrictions on living animals and their products (Rasmussen et al., 2021, Rossi et al., 2017, Garcia-Ispierto and López-Gatius 2016, Salem et al., 2013a). The annual decrease in milk production in the USA due to MAP is about 200 million USD (Losinger 2005). Similarly, in Italy, profit efficiency decreases from 84% to 64% in response to MAP infection in dairy sheep flocks (Sardaro et al., 2017). The cost-efficiency relationship of MAP control programs can be seen by comparing the average annual loss of MAP per cow (79$) with the annual cost of disease control (approximately 30$), according to (Radia et al., 2013).

DISEASE CONTROL

Active shedders excrete MAP in milk and faeces. While milk can infect suckling calves or human consumers, the contaminated faeces can contaminate the udder, the farm utilizes, or the pasture to infect other susceptible animals. Therefore, most programs aim to (1) completely eradicate the pathogen because the survival of few viable MAP in the environment can re-emerge the infection to MAP-free herds via flies, rodents, sewage, stray pets, or wild animals. It was estimated that at least 25 infected (apparently healthy) animals are present for every clinical case borne in a herd. This phenomenon is called ("MAP iceberg effect") (Salem et al., 2013a, Whitlock and Buergelt 1996), (2) to prevent the re-emergence of MAP in free herds, and (3) minimize the infection pressure on susceptible young animals within infected herds (Garcia and Shalloo 2015).Accurate and rapid diagnosis of MAP is the first step in successful control programs. Diagnosis is primarily based on the appearance of clinical symptoms in the herd. However, asymptomatic silent shedders can only be detected by detecting

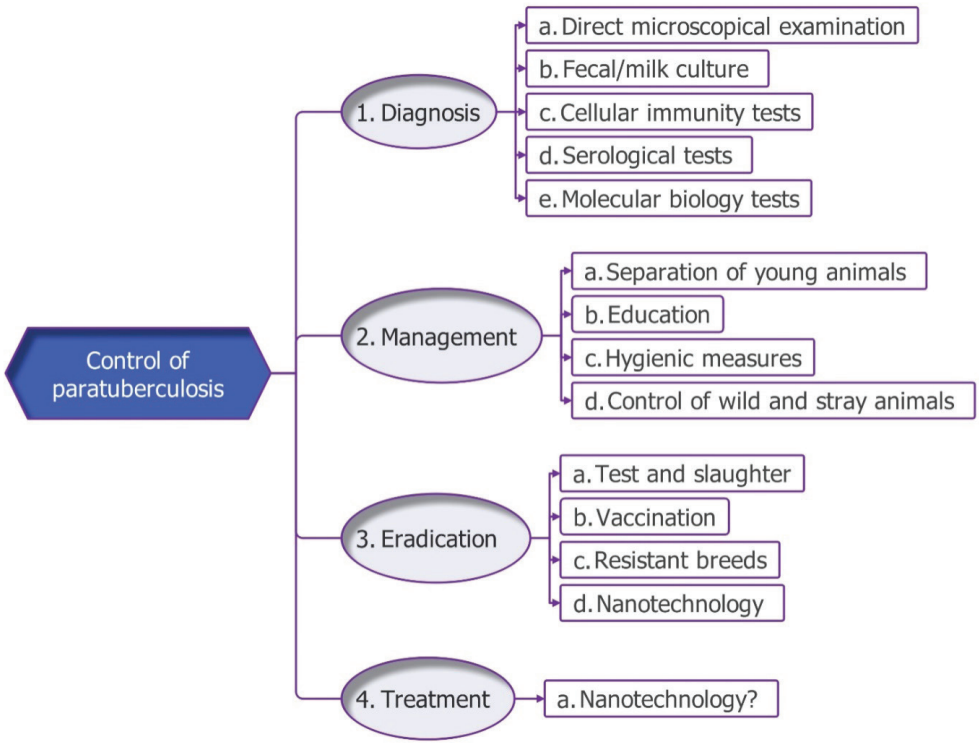

Figure 1: Control of paratuberculosis can be achieved using a cocktail of strategies.

the etiological agent or the resulting immune reaction of the body against invasion (Olsen et al., 2002). Paratuberculosis control can be achieved using a cocktail of strategies (Figure 1).

Management changes

MAP is a robust organism and can only be controlled through the conscious application of management measures. The optimal management strategy for disease control is (1) to avoid direct and indirect contact between old and susceptible young animals directly after birth (Goodger et al., 1996). Only animals from certified herds can be introduced to the herd; routinely used facilities and equipment must be duplicated; and newborn calves are to be separated from their dams and kept on sterile-tested colostrum or milk replacement immediately after birth. (2) Improvements in farm hygiene and manure disposal systems, avoiding the use of manure fertilizers where young calves grace, and the prevention of feed contamination via rodents, birds, or even insects, and(3) regular animal testing (El-Sayed et al., 2013a).

Additional management restrictions must be carried out to protect human consumers. As mentioned previously, pasteurization and UV treatment would not destroy all viable bacilli; therefore, alternative approaches must be developed. For instance, nanotechnology can be applied to remove MAP bacilli from contaminated milk (Mirza Alizadeh et al., 2020, Birkenhauer and Neethirajan 2015, Duncan 2011).

Clinical picture of JD

Paratuberculosis is a long-standing afebrile disease. The main clinical signs in cattle include wasting and watery green diarrhea. Young calves usually attract the disease; however, the clinical signs usually occur in cows older than two years. Exposure of older cows is less likely to result in infection (Khamesipour et al., 2021).

The stages of the disease include stage (1/ silent infection) in young calves in which no clinical signs and no shedding occur. Allergic skin tests or IFN-γ tests can only achieve the diagnosis. This is followed by stage (II/ subclinical infection) characterized by the absence of clinical signs associated with intermittent shedding of the pathogen, usually in low numbers. Repeated culturing or PCR are usually needed to detect such cases. The occurrence of the clinical signs starts in stage (III / clinical cases). The severity of the signs depends on the degree of exposure and the immune system (Tiwari et al., 2006). The signs include the development of gradual but continuous weight loss, and decrease in milk production associated with profuse watery green diarrhea (intermittent

or persistent). However, the appetite and vital signs remain normal. The disease can be diagnosed by fecal culture, PCR or ELISA. Later on, the fourth stage (advanced clinical stage) starts. The exhaustion of blood proteins due to malabsorption and diarrhea leads later on to the development of bottle jaw (submandibular oedema) and cachexia. The animals continue to lose weight and finally die (Manning and Collins 2001). The carcasses are emaciated, and the mucous membranes are pale. Autopsies of the dead animals reveal macroscopic changes in the terminal part of the ileum, which may extend to cover the rest of the intestinal tract. The intestinal tract wall and its afferent lymphatic vessels and the mesentery are usually thickened. The mesenteric lymph nodes are enlarged and may contain caseous or calcified white nodules (Khamesipour et al., 2021, Tiwari et al., 2006).

Diagnosis of JD

The presence of characteristic clinical signs, including emaciation, watery green diarrhea, and decreased productivity,is characteristic for MAP (Salem et al., 2012, Salem et al., 2005).Although the infection starts in young calves up to 6 months of age, the first symptoms usually appear at the earliest between the second and fourth, extremely in the 10th year of life. This is attributed to many reasons, such as the extremely long incubation period of the disease. Infection usually occurs via the faeces - oral route; however, the aerosol infection has also been reported (Whittington et al., 2019).

In addition to the clinical examination, post-mortem findings, cell-mediated immune defense (allergic tests), immunohistochemistry, molecular biological and serological assays, and laboratory/histopathological examination of PM samples are common tools(Karuppusamy et al., 2021, Salem et al., 2012, Salem et al., 2005). Different samples can be used for laboratory diagnosis, including faecal samples, milk, sera, tissue biopsies, and environmental samples. In the past, the complement fixation test was commonly used for serological diagnosis. However, its low sensitivity and specificity make it unreliable for MAP control programs. Similarly, the Agar Gel Immunodiffusion Test has also been used as a rapid, low-cost test in the late stages of infection (Salem et al., 2013a). Nowadays, enzyme-linked immunosorbent assays (ELISAs) are used for the recognition of antibodies in blood and milk samples of clinical cases (Smith et al., 2017, Weber and Schaik 2008, R. J. Whittington et al., 2000). For direct MAP detection, the PCR assay is widely used. Immunohistochemical examination of formalin-fixed, paraffin-embedded tissue biopsies using monoclonal and polyclonal antibodies specific for MAP can also be applied for MAP diagnosis. Generally, combining more than one of the above-mentioned diagnostic methods is recommended to achieve accurate results (Olsen et al., 2002).

i) Direct microscopical fecal examination

MAP is a gram-positive, aerobic, non-motile, non-spore-forming, slow-growing, acid-fast, mycobactin-dependent, facultative intracellular bacillus. Microscopic examination of Ziehl-Neelsen stained faecal smears or intestinal biopsy is a primary rapid and economical diagnostic tool. However, it cannot differentiate between various mycobacterial species and even other acid-fast bacteria,and between viable and dead bacilli (Brees et al., 2000). In addition, the low sensitivity of the test in the early stages, the low number of bacilli in faeces, and their intermittent shedding character limit the use of this method as a reliable diagnostic tool (Whittington et al., 2012, Salem et al., 2005).

ii) Fecal culture

Culture was considered the gold standard for MAP diagnosis in ruminants for many decades. However, it has many limitations, as the long incubation time (up to 16 weeks), high personal expenditure, overwhelming of the grown MAP-colonies by contaminants(e.g. fungal growth), death of some MAP bacilli during the decontamination process, and high cost (Salem et al., 2013a, Collins 2011). Because of its long incubation time(specially in sheep MAP strains) and the highly contaminated nature of the used samples (e.g. faecal samples), the samples must be first decontaminated to eliminate other bacteria, which can overwhelm MAP-colonies (Roller et al., 2020, Bradner et al., 2013).

Moreover, as MAP is a slow-growing microbe, and due to the importance of the time factor to eliminate MAP shedders, time-saving culturing protocols were developed to replace traditional culturing assays (e.g.radiometric-based liquid media). Microbial growth is detected radiometrically (BACTEC) by measuring the liberated CO_2 in the culture. The assay is highly sensitive even for samples containing low MAP numbers and time-saving,especially for very slow-growing strains (Salem et al., 2013a).

Another culture system is now available, namely

the nonradiometric fluorescence-based broth medium (Mycobacteria Growth Indicator Tube (MGIT) System). The media contains modified Middlebrook 7H9 broth with a special sensor embedded in a silicone layer on the bottom of the tubes. Positive samples exhibit an orange-colored fluorescence in response to MAP growth. Confirmation of the grown colonies' identity with PCR is recommended to exclude false-positive samples (Kawaji et al., 2013). The newly developed liquid media assays are rapid,economic, more sensitive, and safe as they do not use radioactive substances(Salem et al., 2017, Fawzy et al., 2015). Different recovery rates of MAP from solid and liquid media were reported, where the growth pattern of different field strains varied according to the media used (Cernicchiaro et al., 2007a, 2007b). To reduce costs, pooling of faecal samples is carried out with a sensitivity rate of 94% compared to the single faecal sample examination at the herd-level (Wells et al., 2003).

iii) Application of in vivo and in vitro cellular immunity tests such as the skin allergic tests (single and comparative intradermal Johnin test; JT) and the interferon (IFN)-γ assay, respectively (Salem et al., 2013a). However,positive JT and the IFN-γ release assay indicate exposure, which does not necessarily result in infection. JT sensitivity and specificity are relatively low, as are the diagnostic sensitivity (48.5% of the fecal positive animals were also positive by skin test) and the specificity (herd-dependent between 58% and 100%)(Collins 1996, Körmendy 1988). In contrast, the IFN-γ assay is applied to demonstrate the cell-mediated immune response in vitro. The test is carried out by stimulating aliquots of heparinized blood with avian PPD. These results in a subsequent release of IFN-γ, which can be measured by IFN-γ ELISA or flow cytometry analysis of peripheral blood IFN-γ-secreting cells. The test has also limited sensitivity (66.7%-93.3%) and specificity (93.5%) (Salem et al., 2013a, Robbe-Austerman et al., 2006, Billman-Jacobe et al., 1992).Older immunological tests as lymphocyte proliferation test are no more used (Rothel et al., 1990).

iv) Serological diagnosis

Although some agglutination tests are commercially available as latex agglutination tests(Singh et al., 2018), ELISA has become the method of choice for primary screening in MAP control programs due to the suitability of sample collection, ability to screen a large number simultaneously, and rapid laboratory turnaround time (Salem et al., 2013a).ELISA shows a good agreement between the results of serum and individual milk samples taken simultaneously (Geisbauer et al., 2007). The sensitivity of ELISA ranges from 0.15 in infected, asymptomatic, non-shedders, and 0.47 in infected, asymptomatic, shedders up to 0.71 in infected, symptomatic shedders. While the presence of shared antigens among saprophytic environmental mycobacteria and MAP limits the test specificity, the test sensitivity is greatly influenced by the phase of the disease, being greatly reduced in subclinical early infected stages (More et al., 2015, Gardner et al., 2011). It is recommended to apply the test at the earliest in animals from the age of 24 months since the detection sensitivity is often lower in younger animals (Anonymus 2012).

In general, test specificity exceeds 99%,while the sensitivity varies depending on the disease stage (Köhler et al., 2008). This fluctuates between 88.2% in herds with strong separators and 4.8% in weak separators (Clark et al., 2008). The identification of the exact number of infected animals is not possible (Lenz et al., 2014).ELISA examination of an entire stock is often extremely cost-intensive (Geue et al., 2007). Therefore, advanced ELISA assays that use pooled milk samples were recently developed. They are rapid, economic and low labor-intensive tools for MAP control programs(Krieger et al., 2021).

As mentioned above, many restrictions limit ELISA use in MAP control programs, including the high cost and the low sensitivity in subclinically infected dairy cattle. Considering the nature of anti-MAP immune responses, serological tests are less useful in detecting subclinical and clinically inconspicuous animals with a low level of circulating antibodies (Magombedze et al., 2017).

The low specificity of commercial systems is attributed to the use of crude MAP antigens obtained by disruption of the bacterium/PPDs in coating the plates, including shared antigens with other mycobacteria. Therefore, false-positive (cross) reactors are common (mainly environmental mycobacteria, MAH and *M. smegmatis*), which can be overcome by the pre-absorption of the sera with *Mycobacterium phlei* to remove any cross-reacting antibodies (Bridges and van Winden 2021, Karuppusamy et al., 2021, Olsen et al., 2002).

Currently, several commercial ELISA systems are available as indirect fluorescent antibody test (i_FAT), Indigenous ELISA test (i_ELISA), and Dot-ELISA

(d_ELISA) (Singh et al., 2018). The improvement of test specificity and sensitivity can be achieved by (1) the involvement of MAP species-specific surface antigens in the manufacturing process (EVELISA system), or the utilization of antigens secreted by young MAP-culture (JTC-ELISA). The latter system has an additional advantage over the former one through being applicable to both serum and milk samples (Salem et al., 2013a).

v) Polymerase Chain Reaction (PCR)

For efficient control programs, accurate rapid diagnostic tools such as PCR are important to rapidly eliminate active and silent shedders (Beinhauerova and Slana 2021).PCR can be used for primary screening, confirmatory purposes, identification of present genotypes for epidemiological studies,and even providing quantitative data. Instead of milk and sera for ELISA, the test uses faecal or environmental samples, which are easier to obtain (Lu et al., 2008). Although the application of PCR for MAP diagnosis is well established, direct application of PCR on faecal samples strongly reduces test sensitivity due to faecal inhibitors. MAP-specific DNA sequences are selected to design MAP-specific primers, including the*IS900* insertion element and *f57* gene, which can be used separately or as multiplex. While *IS900* sequences provide higher sensitivity levels, false-positive results may occur via detecting some non-MAP environmental mycobacteria, thatharbor*IS900* sequence. In contrast, f57 assays have a higher specificity but lower sensitivity. Duplex F57/IC real-time or multiplex PCR systems are recommended to provide high sensitivity and specificity levels. Other MAP-specific sequences may also be used as target sequences as *ISMav*2, 251 and *Hsp* X Sequences. While *F57*, 251 and *Hsp* X sequences are present in a single copy per genome, *ISMav2* sequences occur at least three times. Although all these sequences do not have the same level of sensitivity as primers based on *IS900*, they provide a higher specificity degree(Salem et al., 2017, Salem et al., 2013a, Wells et al., 2006).

For PCR assays, MAPDNA must be extracted by commercial kits or using older protocols based on phenol-chloroform extraction (Cernicchiaro et al., 2007b). To overcome the presence of faecal inhibitors in the sample, the addition of magnetic beads coupled to MAP antibodies or the addition of PCR enhancers to the reaction (as DMSO and Betaine) can be used(-Mason et al., 2001, Marsh and Whittington 2001). In a study by (Stabel et al., 2004), the sensitivity of an *IS900* PCR ranges from 45% (1 CFU/g faeces) to 81% (70 CFU/g faeces), with 90% test specificity in *IS900* based PCRs (Fang et al., 2002, Bögli-Stuber et al., 2005). Both sensitivity and specificity are influenced by the DNA extraction protocol(Sweeney et al., 2006). To save time and cost, collective faecal samples are approved. While specificity remains largely unaffected by pooling, a decrease in sensitivity can be expected due to the "dilution effect"(Wells et al., 2003).

vi) Recombinase Polymerase Amplification (RPA) Assay

The assay is rapid, specific, cost-effective, and requires simple sample preparation steps. Unlike PCR, RPA is an isothermal DNA amplification tool (at 25°C and 42°C). The device used is portable,enabling rapid diagnosis on farms (Daher et al., 2016).Commercial MAP-RPA and real-time RPA assays are now available with 100% and 89.5% specificity and sensitivity, respectively(Hansen et al., 2016).

vii) Phage amplification assay (PA) and plaque PCR

PA is a simple highly sensitive technique that can detect fewer than 100 CFU/mL sample. It detects only viable bacilli (like the culture technique) but quickly (like PCR). The technique was originally developed to detect *Mycobacterium tuberculosis*, however, due to the broad host character of the D29 bacteriophage and its capability to infect different mycobacterial species, the application of the assay was extended to involve MAP diagnosis. The technique depends on the inoculation of the sample with lytic bacteriophage (Beinhauerova and Slana 2021, McNerney et al., 2004).Commercial kits were developed by Biotec Laboratories Limited (UK) as Actiphage™, and PhageTek MB, or *FASTPlaque*TB-*RIF*, *FASTPlaque*-TB-MDRi™, and *FASTPlaque*-TB-Response™to detect antibiotic-resistant isolates (Swift et al., 2020). Lytic phagesare added to the samples and incubated for a few hours to enable the infection of viable MAP with the bacteriophage. Free bacteriophages are chemically killed, and only bacteriophages hidden in the bacilli will survive. Fast-growing non-pathogenic *M. smegmatis* (which is also susceptible to D29 infection) is added to the mixture (Rees and Botsaris 2012, Marei et al., 2003) to trap released bacteriophages. The formation of plaques refers to positive samples. Combining PCR and PA (called plaque PCR) is recommended to confirm the test and exclude false-positive results due to environmental mycobacteria (Grant et al., 2017).

viii) The use of gold nanoparticles (AuNPs) -Oligonucleotides probes (IS*900* gene)

Nano-immuno test has been developed to detect living MAP in milk samples based on MAP-specific antibody-conjugated magnetic nanoparticles and chromogen (Singh et al., 2018, Ganareal et al., 2018). The NPs are mobilized in the sample by an external magnetic field (Singh et al., 2018). AuNP-coupled oligonucleotides were developed to detect MAP DNA, even if a very low number of the bacilli is available. The assay is rapid and can be evaluated in few minutes via colorimetric detection (Ganareal et al., 2018) with a sensitivity level of 91.7% and a specificity of 96.0% (Singh et al., 2018, Ganareal et al., 2018).

TREATMENT

Old trials to treat JD with antibiotics were carried out (St-Jean and Jernigan 1991). Unfortunately, so far, like other mycobacterial diseases in animals, no efficient treatment protocols are available. Despite the economic impact of JD, studies targeting the development of curative agents are directed to public health rather than for veterinary applications (Bates et al., 2019). In humans, MAP infection associated with CD could be successfully treated with antibiotics (Rifabutin, Clarithromycin, Clofazimine, Metronidazole, and Ciprofloxacin) (Agrawal et al., 2020d).

Due to the association between JD and autoimmune diseases, therapeutic approaches of autoimmune diseases (as immunosuppressants or immunomodulators) improved the clinical signs of the disease in humans, without eliminating disease etiology (Garg et al., 2020b).Connecting JD (in ruminants), CD (in humans), and gut microbiota opens the door for future development of aninnovative therapeutic approach for JD/CD (Khanna and Le Raffals 2017, Marie-Eve Fecteau et al., 2016). Correction of gut dysbiosis through the administration of probiotics (e.g. *E.coli Nissle*1917, *Clostridium butyricum MIYAIRI 588*, *and Bifidobacterium longum/Synergy 1*) or transplantation of fecal microbiota is promising in the treatment of IBD and CD (Agrawal et al., 2020c, Honap et al., 2020a, 2020b, Borody et al., 2019, Gevers et al., 2014, Liang et al., 2014, Matsuoka and Kanai 2014, Wang et al., 2013). The administrated probiotics can re-establish the microbial balance by increasing the numbers of *Faecalibacterium prausnitzii, Akkermansia muciniphila* and *Roseburia* species, decreasing the number of *MAP*, *Yersinia, Clostridium difficile, Desulfovibrio, Bilophila wadsworthia,* pathogenic *E. coli, Salmonella,* and *Listeria* spp in the gut and eliminating the pro-inflammatory *Actinobacteria* and *Proteobacteria* (Yoshimatsu et al., 2021, Singh et al., 2020).Similarly,administration of pluripotent stem cells could completely cure CD/IBD patients. The stem cell could simultaneously correct immunological abnormalities, repair the intestinal ulcers, and restore normal gut functionality. Combinations of stem cell therapy and the correction of microbial dysbiosis represents an ideal therapeutic approach for CD patients in the near future (Singh 2010).

Advances in nanotechnology have launched a revolution in medical fields and improved JD diagnosis, treatment, and prevention(Agrawal et al., 2020a). They can eliminate intracellular pathogens or those with high antibiotic resistance profiles as mycobacterial diseases (El-Sayed and Kamel 2020b). Recently, special gallium nanoparticles (NP) were developedto inhibit mycobacterial growth and modulate host macrophage cytokine production (El-Sayed and Kamel 2020a, Choi et al., 2019).

ERADICATION:

Current control programs are designed to enhance on-farm biosecurity and to combine managemental and educational measures with local test-and-cull programs. However, the exact goal of the selected program varies according to the circumstances of each country which ranges from keeping the disease under control to the complete elimination of the pathogen at the national level (Okuni et al., 2020, Salem et al., 2013a, Lu et al., 2008, Jubb 2000).

It is also important to certify MAP-free herds. Cows originating from such herds can be freely sold/exported. However, these herds must be regularly tested to guarantee their MAP-free status. Herd certification requires periodic negative test results of herd individual, collective samples, and environmental samples (e.g. boot-swabs). A growing number of negative boot swab results raises the probability of a negative MAP status in a given herd (Koechler et al., 2017). However, such programs usually face considerable obstacles,including(1) the long incubation period, (2) persistence of microbe in the environment, in wild ruminants, birds, and even insects, (3) asymptomatic shedders in the herd,which represent a constant source of infection for the healthy (young) animals. In addition, the presence of intermediate shedders and false negative/positive cases implicates the problem and makes (test and slaughter) decision

difficult, (4) absence of reliable, highly sensitive, and specific diagnostic tool, (5) the high cost of testing all animals (Whittington et al., 2019, Salem et al., 2013b),(6) absence of vaccination policy to avoid interference with BTB diagnosis, (7) unavailability of medication, (8) the lack of epidemiological data and the knowledge about dominant MAP genotypes in many countries. These data are important as only few MAP genotypes are responsible for mass herd infections or capable of human infections, (9) the limited interest of farmers to participate in control programs due to the costs, long duration of such programs over years, and the intensive workload,and (10) the lack of resources to continue the eradication programs in developing countries (Whittington et al., 2019, Salem et al., 2013a).

As accurate diagnosis is necessary to minimize unnecessary culling of healthy animals or the escape of infected animals, it is therefore recommended to combine more than one diagnostic tool such as ELISA (primary screening) and PCR (confirmation of positive cases)(Weber 2006).The average success of the programs is estimated to be 73% among various programs. The strictness of the programs varies among different countries, being voluntary in some countries and obligatory in others(Garvey 2020, McAloon et al., 2019, Salem et al., 2017, Salem et al., 2013a).Some control programs tolerate an "acceptable level of risk" instead of complete eradication of the pathogen through the application of risk-based control strategies. Participation in such programs is based on a combination of several risk factors in relation to herd productivity and health parameters. The prevention of new infections is a major condition for the successful application of test-and-cull control programs. The application of strict hygienic parameters to prevent contact between the pathogen and susceptible calves reduces at least 10% of MAP prevalence within few years (Kudahl et al., 2008, Weber 2006).

Education programs of farmers are important to learn how to minimize contact between adults and young calves, the immediate separation of the newborn calves from the adult cows, how to efficiently clean udders and legs before parturition, to prevent calves from sucking infected milk, avoid manure fertilization of fields to prevent calves from coming in contact with adult faeces, application of strict hygienic measures in the calf yards, duplication of used facilities and equipment, control of rodents and stray pets in the farm, and newly purchased animals must be tested and should originate from certified MAP-free herds.

CULLING: TEST AND SLAUGHTER POLICY:

Culling of infected animals takes place following the detection of MAP in faeces (PCR/culture),or MAP antibodies (ELISA) to prevent further shedding of the pathogen in the surrounding of young susceptible animals (Whitlock 2000, Zimmer et al., 1999).However, this concept(1) does not take the "pass through animals" into consideration, and (2) the use of culture wastes valuable time till the colonies grow, during this period, the shedders continue to infect new animals. The problem can be more obvious in herds with super shedders (cows that shed between 10,000 and 10 million MAP bacilli/g faeces). This can be overcome by replacing culture method with PCR (Manning et al., 2003). Alternatively, culling is carried out in accordance with the results obtained by serological screening with ELISA (Collins et al., 2006). PCR assay is the most suitable protocol in control programs due to its high sensitivity and specificity. It enables early detection of infected cows, possibly before they develop antibodies. However, the high cost and the need for well-equipped labs and well-trained personals limit the wide application of PCR-based culling policy (Salem et al., 2013a, Alinovi et al., 2009).

COLLECTIVE SAMPLING USED IN FREE AREAS AND SAMPLING METHODS

The use of boot swab samples in cattle farms has become more common to evaluate MAP status. The test reproductivity was proven in various studies (Koechler et al., 2017). Recently, the use of environmental samples was approved for large-scale MAP screening projects (Donat et al., 2016, Lombard 2011, Smith et al., 2011, Eisenberg et al., 2010, Bolster et al., 2009, Pillars et al., 2009b, Berghaus et al., 2006, Crawford et al., 2006, Raizman et al., 2004, Manning et al., 2003).The samples include bedding, manure, soil, bulk milk or milk filter samples (El-Sayed et al., 2013a, Salem et al., 2013b) (table 2). It is also important to collect samples from insects, stray pets, and wild animals near the herds to ensure and maintain the pathogen's complete absence from the surrounding (Salem et al., 2017). The sensitivity of detecting infected herds depends on the location and the number of environmental samples taken (Pillars et al., 2009a).

In a pilot project carried out by our team in Germany, environmental samples from the barn area (taken with the help of a sock swab) were examined.

Table 2: Animals, humans and the environment from which the MAP was isolated.

MAP isolated from	Reference
Human	(Timms et al., 2015)
Primates (Mandrill, Stumptail macaque, Common marmoset, Rhesus macaques, Cottontop tamarins, Black-and-white ruffed lemurs)	(More et al., 2017)
Cattle	(Salem et al., 2005a)
Zebu cattle, Sheep, Goats	(Chiodini et al., 1984)
Rocky mountain goat, Pygmy goat, Dwarf goats, Stone buck, Mouflon sheep, Bighorn sheep, Barbary sheep, Cameroon sheep, Antelope kudu, Saiga antelope	(More et al., 2017)
Buffaloes	(Abdellrazeq et al., 2014)
Alpaca	(Ridge et al., 1995)
Lama	(Salgado et al., 2009)
Camel	(Salem et al., 2017)
Alpine ibex	(Ferroglio et al., 2000)
Deer	(Salgado et al., 2017)
Fallow deer	(Machackova et al., 2004)
White-tailed deer	(Chiodini and van Kruiningen 1983)
Red and roe (Capreolus capreolus) deer	(Sharp et al.,)
Bighorn sheep	(Williams et al., 1979)
Tule elk	(Jessup and Abbas 1981)
Bison	(Deutz et al., 2005a)
Chamois	(Deutz et al., 2005b)
Yak	(Geilhausen)
Pigs	(Boadella et al., 2011)
Reptilian (snakes, chelonians, and lizards)	(Soldati et al., 2004)
Earth worm	(Fischer et al., 2004b)
Different species of Flies such as Musca spp. and Stomoxys	(Fischer et al., 2001, Fischer et al., 2005, Manning and Collins 2010)
Beetles	(Fischer et al., 2004b)
Blowflies	(Fischer et al., 2004a)
Fox, stoat, weasel, crow, rook, jackdaw, rat, wood mouse, hare, and badger	(Beard et al., 2001b)
Dog, cat	(Kukanich et al., 2013, Salem et al., 2019)
Stripen skunk, Raccoon,	(Corn et al., 2005)
Badger, stoat, weasel	(Daniels et al., 2003)
Brown bear	(Kopecna et al., 2006)
Brown hare, Mountain hare, Eastern cottonail	(Corn et al., 2005, Deutz et al., 2005c)
Rabbits	(Mokresh and Butler 1990)
Hamsters	(Hirch 1956)
lemmings	(Larsen and Miller 1979)
Guinea pigs	(Francis 1943)
Mice	(Harding 1959)
Rat	(Florou et al., 2008)
Ferret	(Lisle et al., 2008)
Hispid cotton rat and Norway rat	(Corn et al., 2005)
Chicken	(Sattar et al., 2021)
Birds (Buzzard, Crow, pigeon, Wood pigeon, sparrow, Rook, Jackdaw, Pheasant,	(Corn et al., 2005, Beard et al., 2001a)
European starling, Common snipe	(Corn et al., 2005)
Chicken	(Larsen et al., 1972)
Diamant sparrow	(Miranda et al., 2009)
Manure, environmental samples and milk filters	(El-Sayed et al., 2013a)

The sock swab consisted of a sterile gauze material, which was pulled over a disposable boot. The sampler moved in a meandering manner over the main shoot paths in the barn. The sock swab was then examined both culturally and using qPCR for MAP. The results showed a good agreement (90.6%) with the farm status as determined by single milk, blood, and single animal faecal samples (Eisenberg et al., 2013). The obtained data from the project are still under evaluation and preparation for publication.

In an elaborate study, a total of 77 German dairy herds were examined using a sock swab and a liquid manure sample. Inner herd prevalence had previously been determined by cultural-bacteriological examination of single faecal samples and was between 0 and 46.8% (median 4.9%). As a result, it was possible with a one-time examination, herds with an inner herd prevalence of at least 3.3% (with a combined examination of sock swab and liquid manure samples) or 5.9% (with only examination of the sock swab) with 90% sensitivity and 100% specificity to be recognized as infected. Repeated examinations (e.g., twice a year) could increase the sensitivity with the same specificity of this method (Donat et al., 2014).

IMMUNIZATION:

Vaccination is one of the most important elements in control programs. Although commercial MAP vaccines are available, there are many reasons why limited attention is directed toward developing a MAP vaccine (Table 3). They provide only partial protection of the population (Sandeep K. Gupta et al.,, Bannantine and Talaat 2015),and may interfere with allergic and serological diagnosis of bovine TB(Doré et al., 2012, Salem et al., 2013a, Bastida and Juste 2011). The use of DIVA MAP vaccine or the usage of comparative intradermal tuberculin test to replace the single intradermal tuberculin test enables the option of mass vaccination for disease control (Luo and Buck 2020, Palacios et al., 2019, Barry et al., 2011). DIVA MAP vaccines were tested to overcome the previously mentioned diagnostic problems. The genetic marker of the vaccinal strains was made through the replacement of the (*MAP1693c*) with a library of different epitope-tagged immunogenic genes (*pepA*) (Luo and Buck 2020).

Currently, oil adjuvant killed whole culture vaccines, subunit, live attenuated vaccine delivered by Salmonella, and living avirulent vaccines are being developed. The pilot studies showed promising results as they advocate both cellular and humoral immunity, beside the reduction of pathogen shedding (Ugochukwu et al., 2020, Bannantine et al., 2014a, Bannantine et al., 2014b, Faisal et al., 2013, Johnston et al., 2010).

Attempts to develop whole cell inactivated, fractionated subunit, recombinant and even DNA vaccines are under evaluation. To achieve the best results, vaccines must be administered to young calves (Kathaperumal et al., 2009, Sechi et al., 2006b).Gamma interferon release assay and Enferplex™ TB assay (Enfer Scientific, Naas, County Kildare, Ireland) were developed to differentiate between vaccinated and infected animals, however, optimization of these

Table 3: Available worldwide commercial vaccines used for controlling paratuberculosis with their adjuvants, biotype and vaccine strain used

Name of vaccine	Countries	Adjuvants, biotype and vaccine strain
Phylaxia (Phylaxia Veterinary Biologicals Company)	Hungary	Oil type killed vaccine of 5889 Bergey strain
Gudair (Zoetis Pfizer)	Australia	Oil emulsion killed vaccine from 318F strain
Aqua Vax MAP(AquaVax Ltd)	New Zealand	Water based (saline) live attenuated vaccine from 316F strain
Weybridge Vaccine (Animal Health and Veterinary Laboratories Agency, Weybridge laboratory)	United Kingdom	Weybridge vaccine live attenuated vaccine from 316F strain
Mycopar (Boehringer Ingelheim Animal Health)	Germany	Oil emulsion inactivated vaccine from whole cell bacterin
Neoparasec (Merial NZ Ltd.)	France	Oil type live attenuated vaccine from Freeze dried live MAP
Bio-JD Oil & Gel (BiovetPvt. Ltd.)	India	Aluminium hydroxide gel (Gudair, Spain), Gerbu adjuvant (Gerbubiotechnik, Germany) Inactivated vaccine from native MAP strain (S 5)'Indian Bison type'
Silirum (Pfizer CSL)	Australia	Oil emulsion killed vaccine from 318F strain
Fromm (Fromm Laboratories)	USA	Oil type (Freund`s complete) killed vaccine from MAP strain 18
Lio-Johne (Ovejero)	Spain	Oil type live attenuated vaccine of 316F strain

test are still required(Barry et al., 2011). The differentiation between infected and diseased animals can also be achieved via modification of the allergic tests. MAP vaccine in sheep appears not to be of economic relevance (Eppleston and Windsor 2007).

VACCINE TYPES

Both live (non-attenuated and attenuated), killed whole cell vaccines,and to less extent, subunit vaccines (sonicated bacteria, bacterial cell fractions or recombinant MAP antigens) were tested for the control of JD but delivered a low degree of protection (Kathaperumal et al., 2009, Koets et al., 2006). More recently, DNA vaccines (mammalian expression vectors containing MAP genes) have also been tested in mice, sheep,and humans but not in cattle (Kadam et al., 2009, Park et al., 2008, Roupie et al., 2008, Bull et al., 2007, Sechi et al., 2006a, Huntley et al., 2005, Velaz-Faircloth et al., 1999). Most MAP vaccine formulations have been based on mycobacteria and a water-in-oil emulsion (olive, mineral, liquid, paraffin, etc). Sometimes irritable oils are used to enhance blood flow to the injection site and consequently improve the immune response. The adjuvants establish a focus of inflammation where the antigens stimulate the host immune system permanently so that revaccination is not required (Bastida and Juste 2011).

Recent trials of nano-vaccines delivered promising results. The vaccine contains MAP antigens and whole culture lysate encapsulated by nanoparticles. The administration of a single dose of polyanhydride-based NP could significantly reduce the bacterial load and provide a protective immune response against invading MAP. They are well-tolerated, safe for use in dairy animals and provide sustained immunity against MAP infection (Thukral et al., 2020).

BACILLE CALMETTE-GUERIN (BCG)

BCG, a live attenuated vaccine, is widely used in many countries to protect against human tuberculosis and other mycobacterial infections as leprosy and Buruli's ulcer. It acts as an immunomodulating agent which can help patients suffering from various autoimmune/inflammatory diseases, including CD, sarcoidosis, Blau syndrome, Hashimoto's thyroiditis, autoimmune diabetes, multiple sclerosis, rheumatoid arthritis, lupus, Parkinson's and Alzheimer's diseases, and even patient with bladder cancer (Dow 2020). BCG vaccination produces a nonspecific protective effect against non-related pathogens like viruses as it modulates the immune response (trained immunity) and prolongs the production of IFN-γ, IL-17, and IL-22and to heterologous Th1/Th17 responses (Kleinnijenhuis et al., 2013). Therefore, it was reported that BCG possibly decreases the mortalities in COVID-19 patients by modulating the immune response of the patients. This can explain the differences in COVID-19 mortalities among countries still using BCG in comparison to industrial countries (Ozdemir et al.,, Curtis et al., 2020, Desouky 2020). BCG was also shown to protect against MAP not only in dairy animals (Dow 2020), but also in humans(Collins et al., 2000).

EXCLUSION OF GENETICALLY SUSCEPTIBLE BREEDS FROM THE HERDS

Published data argue the link between MAP susceptibility, disease severity, and genetic predisposing factors (Begg et al., 2017, Reddacliff et al., 2005, Koets et al., 2000). Differences in disease susceptibility and immune response could be recognized even among individual animals within the same breed in beef cattle (Çınar et al., 2020, Juste et al., 2018, Begg et al., 2017), dairy cows (Berry et al. 2010),small ruminants (Mortensen et al., 2004, Sorge et al., 2011), and deer (Vázquez et al., 2014).Genome analysis revealed a link between MAP susceptibility and the presence of heterozygous alleles in cis-eQTL-rs43744169 (T/C), cis-eQTL-rs110345285 (C/C), and cis-eQTL rs109859270 (C/T), which influence the expression level of eukaryotic elongation factor 1-α2 (eEF1A2), MDS1 and EVI1 of (MECOM) complex (Canive et al., 2021). Animals harboring these genetic markers should be excluded from the herds, and only resistant animals are reared as a part of running JD control programs (Ruiz-Larrañaga et al., 2010a, Ruiz-Larrañaga et al., 2010b).

CONCLUSION

The economic and public health impacts of JD are underestimated. Active MAP eradication programs are now running in several countries with various degrees of success. The robustness of the pathogen under severe environmental conditions, the absence of curative treatment and an efficient vaccination policy, and the ease of re-introduction of the disease in free herds, all these factors make international cooperation very important to carry out long-term eradication programs.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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