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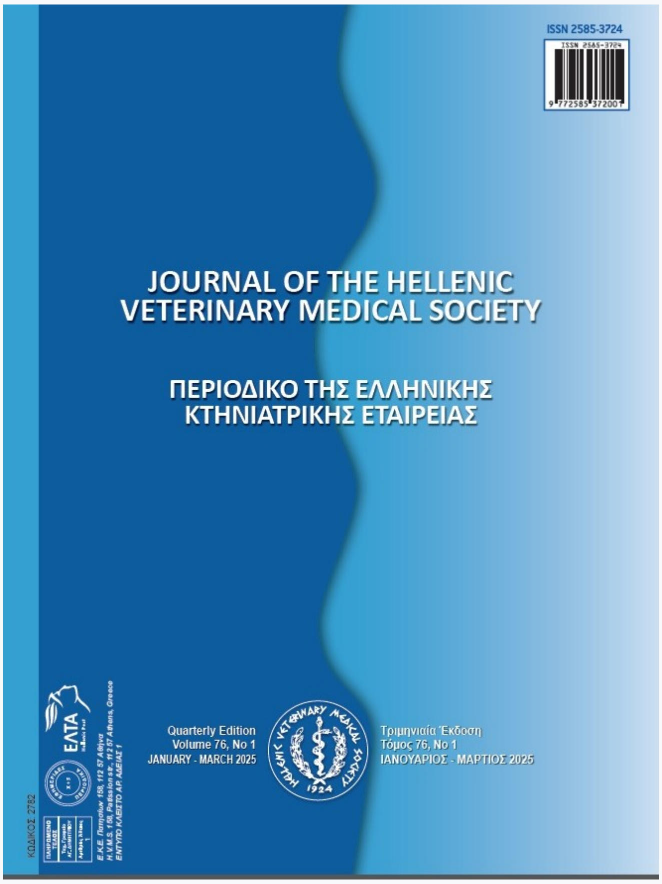

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Research article
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Paratuberculosis: The Trojan in genetic resources of dairy cattle

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ABSTRACT: *Mycobacterium avium subspecies paratuberculosis* is the main cause of paratuberculosis or Johne's disease, an intestinal granulomatous infection among ruminants. This review will focus on Johne's disease in dairy cattle. This disease has become a significant problem for dairy breeders due to its global spread and is considered a nightmare for them. The disease has a long incubation period and is highly transmissible from infected animals to others, making it difficult to detect until a large number of animals are already infected. This leads to significant financial and economic losses for breeders, impacting the economic network of each country and leading to a loss for export programs of producing countries. The lack of an accurate diagnostic method has made the management and prevention of Johne's disease difficult. There is growing interest in managing and reducing the disease's side effects and efforts to find accurate, fast, and readily available diagnostic methods. This study aims to review various aspects of the economic losses and the threat of this infection to genetic resources and breeding programs, as well as to introduce novel physical diagnostic methods to prevent losses caused by this disease.

Keywords: Johne's disease; genetic resource; diagnostic methods; economic losses

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INTRODUCTION

Due to the growing global population, ensuring access to healthy and sustainable food is a top priority for every country worldwide. Achieving this goal is based on the food pyramid, which is a fundamental tool for planning proper nutrition in society. The food pyramid prioritizes all food groups, all of which are derived from the activities of the agricultural sector. In recent years, there has been a limitation in the activity of this sector, leading to an increased need to focus on its concentration and industrialization. Meanwhile, the concentration and industrialized production of livestock and poultry breeding has a long history due to the high demand for these products, which play a crucial role in supplying two parts of the food pyramid. In line with the sustainable development goals of the United Nations, there is a push for environmentally friendly animal breeding systems to interact with four key goals: 1) Poverty Eradication, 2) Ending Hunger, 3) Adaptation to Climate Change and 4) Access to Clean and Hygienic Water. This is to achieve: 1) Adaptation and reduction of climate change effects, 2) Increasing water quality and recycling, 3) Increasing biodiversity, and 4) Development and food security (Lal, 2020).

To achieve stability in herd health and production, as well as high performance and reliable profit, it is essential to focus on ensuring herd health conditions, implementing precise nutrition programs, maintaining consistent breeding programs, and following economic principles. Genetic factors play a crucial role in this, such as the type of breed, preservation, and promotion of genetic resources with valuable economic traits, elimination of risk factors, and creating favorable conditions for maximum expression of genes effective in production.

When it comes to ruminant animals, the investigated traits are divided into two categories: productive traits, such as milk and meat production, and functional traits related to health and reproductive efficiency in both sexes. Production traits generally have medium heritability, while infertility-related traits have low heritability. Therefore, the expression of these traits is more influenced by management and environmental factors than genetic factors. (Miglior et al., 2017). Fertility rate, as one of the functional traits, has a significant impact on the herd's profitability. One factor that decreases the fertility rate in the herd is Johne's disease (Arnott et al., 2015).

AN OVERVIEW OF JOHNE'S DISEASE

MAP and Johne's disease

The World Organization for Animal Health has classified Johne's disease as a group B disease. The cause of the disease is transmissible and is significant from a socioeconomic and public health perspective (OIE, 2012). This global animal disorder is caused by Mycobacterium avium subspecies Paratuberculosis (MAP), which is a gram-positive acid-fast bacterium and a member of the Mycobacterium avium complex. It frequently affects ruminants and has the ability to spread to the entire herd, leading to outbreaks (OIE Terrestrial Manual 2021- PARATUBERCULOSIS (JOHNE'S DISEASE)2021.pdf, 2021; Pickrodt et al., 2023). One of the prominent attributes of this strain is its ability to gain access to a susceptible host, evade host defense mechanisms, and rapidly but stealthily propagate to other hosts (Byrne et al., 2023).

Ways to spread MAP

The agent of Johne's disease is transmitted from animal to animal in both horizontal and vertical ways. In horizontal transmission, MAP is mainly transmitted by the fecal-oral route. It is especially spread through fecal contamination of the udder, pasture, water, food, colostrum, and aerosol. These factors may carry bacteria to an environmental niche from which it could spread to healthy cattle. In vertical transmission, MAP is mainly transmitted from the infected dam to the embryo through the placenta (Lee et al., 2023). Following exposure to infected food, the initial site of paratuberculosis colonization is in the Peyer's patches in the ileum and jejunum, which are lymphoid tissues in the intestinal mucosa and submucosa (Johnson et al., 2022). Then, the strain may spread to the mucosal lamina propria and systemically disseminate (Schrott et al., 2023). Finally, it will be possible to spread the strain's colonies through feces, potentially infecting other animals (Ssekitoleko et al., 2021). Although the infection initially starts locally, it can progress to a systemic pattern as chronic granulomatous enteritis, ultimately leading to the death of the animal. The pathogenesis of paratuberculosis is similar to other types of mycobacterial diseases, such as tuberculosis (Marquetoux et al., 2019; Correa-Valencia et al., 2021). From a pathophysiological point of view, paratuberculosis is an intracellular pathogen with the ability to induce immunological response and, therefore, is commonly considered a subclinical infection. However, due to the possibility of creating an animal epidemic, it may impose a heavy financial burden on the veterinary community of any country (Rangel et al., 2015). The majority of ruminant livestock species, whether domestic or wild, can be affected by paratuberculosis. This infection is widespread and almost no country or region has been spared from its threat. Paratuberculosis transmission is insidious and can occur without any symptoms (Li et al., 2016; McAloon et al., 2019). Therefore, in many cases, the diagnosis of the disease is late and time occurs that has left its complications, and this problem doubles the financial burden caused by the disease. On the other hand, the incubation period of the disease is too long and this issue will also encourage the disease to be hidden for a long time in the herd (Hussain et al., 2016). Based on this, Johne's disease is classified into four stages, and in the following, explanations are provided about each.

Stages of Johne's disease

Johne's disease is classified into four stages: silent, subclinical, clinical, and advanced. It may affect calves from the embryonic period to the first months of birth, although its clinical symptoms may not be revealed for years. Other animals can be exposed to contamination from the feces of infected animals, the environment, food, and milk. This increases the spread of the disease in the herd so that for each animal in the final stage of the disease, there are 1 to 2 animals in the clinical stage, 6 to 8 animals in the subclinical stage, and 15 to 25 animals in the initial stage of the disease (Fecteau, 2018). This point emphasizes the need to pay special attention to Johne's disease in preserving genetic resources, so it can be called the Trojan (Figure 1).

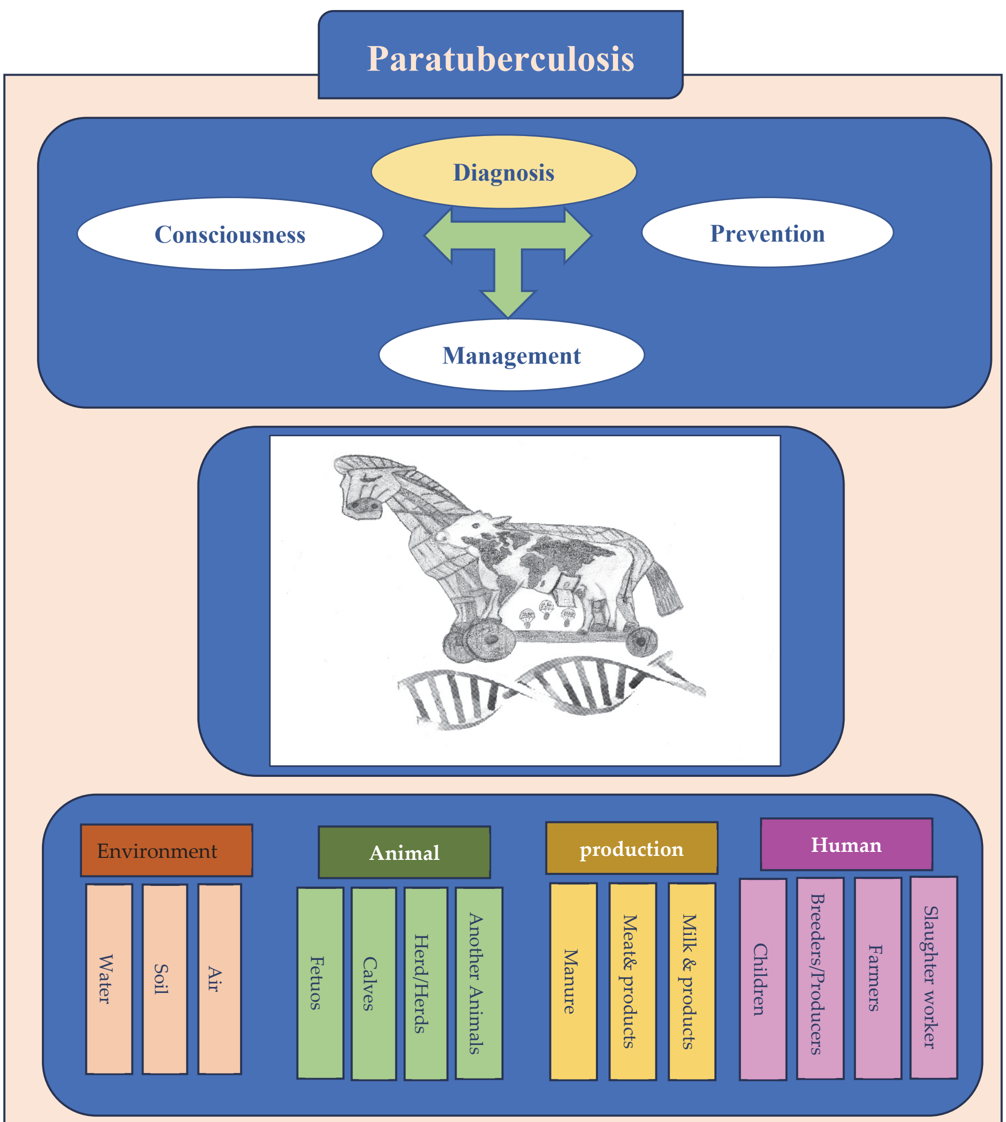

Figure 1. The aspects of Paratuberculosis. Paratuberculosis like Trojan in dairy cattle herds.

Kind of breeding

Another point is the higher prevalence and incidence of Johne's disease in dairy herds compared to beef herds due to the intensive breeding of dairy cattle. Moreover, beef cattle are mostly slaughtered before they become symptomatic through contracting this disease (Rindi & Garzelli, 2014). This underscores the significance of understanding this infection and its impact on society's economy.

Map resistance

As another important point, paratuberculosis is tolerant of acidic soils and low temperatures, including freezing, but appears to be less resistant in hot and dry climates (Mortier et al., 2015; Zhang et al., 2016). Paratuberculosis protected from sunlight lasted up to 55 weeks in a fully shaded dry environment (Karuppusamy et al., 2019). Therefore, it is obvious that we will witness the spread of this disease in different climates. Even though the quality and extent of vegetation in the area are very effective on the prevalence and durability of the infection, the reduction of vegetation and grassland in the area can reduce the survival of the infected even for weeks (Koets et al., 2015).

Host genetic resistance

Another important indicator in contracting the disease is the breed or the genetic origin of the animal so some livestock breeds are more resistant to Johne's disease and as a result less likely to develop clinical paratuberculosis in other words, polymorphisms in innate immune genes have been found to influence resistance and susceptibility to the Johne's Disease. Candidate genes identified across studies overlap with those found in Crohn's disease and tuberculosis including; Solute carrier family 11member one gene (SLC11A1), Nucleotide-binding-oligomerization domain-containing gene 2 (NOD2), Major histocompatibility complex type II (MHC-II), and Toll-like receptor (TLR) genes (Kravitz et al., 2021).

The investigation has reviewed several studies to identify Quantitative Trait Loci (QTLs) related to Johne's disease. The findings indicate that different QTLs have been identified based on the method of disease diagnosis. For example, a study using serum and fecal cultures identified the QTL of Bos Taurus Atosome(BTA)20. QTLs on BTA 5, BTA4, BTA18, and BTA28 were identified based on milk ELISA response. A QTL on BTA3 related to sensitivity to MAp was identified based on tissue culture. Additionally, a QTL9 was identified based on tissue culture and feces. Furthermore, using the MAP antibody ELISA test, QTLs on BTA1, BTA5, BTA6, BTA7, BTA10, and BTA11 were identified. Finally, based on serum ELISA and stool culture, QTLs on BTA1, BTA2, BTA6, BTA7, BTA17, and BTA29 were identified (Mallikarjunappa et al., 2021). Based on these findings, the method of disease diagnosis greatly impacts the identification of effective QTLs in Johne's disease and genomics studies aimed at identifying QTLs for disease resistance or susceptibility. Accurate disease diagnosis methods are essential for selecting animals with resistant genes.

Immunology of Johne's disease

As mentioned, the basic pathology of Johne's disease is the stimulation of the host's immune system and the occurrence of sometimes severe immune responses (Hussain et al., 2016) in this regard, the infection can infect a set of cells of the immune system. As the first immunological effect, the bacterium may infect macrophages followed by stimulating T-helper lymphocytes that result in the secretion of some specific pro-inflammatory cytokines such as interleukin 2, interleukin 12, interleukin 10, interleukin 13, interferon-gamma, and tumor necrosis factor-alpha (Määttänen et al., 2013; Johnson et al., 2014; DeKuiper & Coussens, 2019). Such cytokines are responsible for orchestrating both humoral and cell-mediated immune responses. The initial immune response to this infection involves numerous infected macrophages with increased amounts of adhesion molecules, leading to granuloma formation in which bacilli remain isolated for a long time (Shandilya et al., 2023) The animal has no clinical symptoms in this condition and may remain in the subclinical stage for a long time (up to five years), while the bacilli are contained in granulomas and macrophages (Karunasena et al., 2014). The duration of incubation and the emergence of symptoms of the disease are completely unknown and accordingly, it will be very difficult to plan for the management of the spread of the disease and its clinical control (Magombedze et al., 2015). Another point is that sometimes the body's immune cells cannot defeat bacteria, which leads to rapid intracellular multiplication of their cells, which together with the high production of immunoglobulin G1 antibodies leads to a late humoral response, aggravating the severity of the infection (Frie et al., 2017; Davis et al., 2021). Therefore, for separating infected animals into two clinical and subclinical levels need for an accurate and fast diagnostic method is evident.

Spread and epidemic Johne's disease controlling and preventing factors

In general, there are two important methods in controlling the spread and epidemic caused by this infectious disease, which are very effective in the economic aspects and the financial burden. The first factor is to pay attention to infection control ways and operating instructions and the second factor is to prevent of transmission infection in the herd. Control of the infection is the first step to prevent the spreading disease. Unfortunately, the identification of infection in the herd takes place when the bacterial strain has already spread in it (Karuppusamy et al., 2021). Therefore, rapid identification of the infected animals and separating them, as well as vaccination of its members, will be the first step in controlling the spread of infection. Additionally, the entry of infected animals into the herd will be a very important risk factor for the spread of bacteria (Chaubey et al., 2016). Unfortunately, farmers' information about the risk of infection is little. In this regard, the first way to control the infection is to identify followed by eliminating infected animals clinically and even sub-clinically (Mortier et al., 2015) However, due to the lack of timely identification and the high durability of the strain in the environment, it may be not possible to eradicate paratuberculosis in the short term (Britton et al., 2016).

The second step in controlling disease spread is to prevent paratuberculosis transmission within the herd by enhancing on-farm biosecurity, especially during the rearing of young calves. In this regard, preventing calves from contacting the feces of adult cows is the optimal approach that avoids fecal-oral transmission. It seems that the use of both strategies will limit the spread of infection and minimize the risk of its transmission to herd members (Windsor, 2015; Jain et al., 2021). In addition to the above two steps, quick culling of the infected animals from the herd should be considered as soon as possible (Verdugo et al., 2023). The second factor in infection control and prevention is the early vaccination of ruminants. This preventive strategy can effectively reduce the incidence of paratuberculosis, delay disease onset, reduce the likelihood of fecal shedding of infection, and ultimately reduce the risk for disease transmission (Roller et al., 2020). Another important point is the correct use of tests and diagnostic approaches for infection and its spread in the shortest time possible (Gilardoni et al., 2016). Diagnostic tests for infection are designed and used mainly on two bases including those for tracking the infection and tests for identifying the host immune response against the bacterium. To diagnose paratuberculosis strain, two techniques of bacterial culture and tracking its molecular component by polymerase chain reaction technique are applicable (Verdugo et al., 2023). To assess the host immune response, the molecular techniques of enzyme-linked immunosorbent assay (ELISA), complement fixation test (CFT), and agar gel immunodiffusion (AGID) are frequently used (Nájera-Rivera et al., 2023). However, the accuracy and sensitivity of the mentioned tests are very different, and it is sometimes recommended to use a set of tests, especially in more advanced stages of the disease. However, it is notable that the choice between tests can be related to costs and logistics (Klepp et al., 2023). Of course, it should be kept in mind that the mentioned molecular tests are very effective in early screening and tracking, and a definitive and accurate diagnosis of the disease, especially its tissue effects, will be possible based on histopathological studies.

As a result, achieving an accurate diagnosis method for detecting the health of infected animals according to the disease agent and the antibody produced, and being able to show the state of the animal in each stage of the disease, is a global necessity.

THE ECONOMIC IMPACTS OF PARATUBERCULOSIS

The economic losses caused by paratuberculosis can overshadow the management and control approaches of the disease and adversely affect the governmental industry's decision-making. These losses contain direct and indirect effects (Barratt et al., 2019).

Direct effects contain visible and invisible effects. Visible effects of Paratuberculosis infection, such as reduced growth, reduction of weight, lower meat and milk production, premature elimination, increase in mortality, and costs due to its compensation are among the economic losses of Johne's disease on dairy cattle breeding herds. The invisible effects losses of the disease include reduced fertility or infertility, costs of disease control, costs of diagnostic tests, abortions, births of infected calves and susceptibility to other diseases, and veterinary costs (Barratt et al., 2019). These losses come from the fact that by exterminating the infected animals, the production of milk and also meat from its slaughtering is significantly reduced (Dane et al., 2023). Pre-slaughter losses include significant reductions in milk production, funding for the follow-up treatment of mastitis, as well as the costs related to diagnostic tests. Since this infection will be associated with a significant reduction in body weight, the slaughter value of infected cattle is also reduced (Whittington et al., 2019; Garvey, 2020). The most important costs related to slaughtering will also include financing the costs due to the absence of healthy animal carcasses (Garcia & Shalloo, 2015).

Indirect effects include disease control costs, revenue foregone from restricted market access, export losses, losses to other sectors in the supply chain and consumers, the impact on the health and welfare of animals, marketing and public health-related issues, reduction in productivity, loss of business and market, and decrease in market value and food insecurity. One of the important indirect effects is a decrease in the rate of genetic improvement due to the increase in elimination rate and elimination of super animals, which is a threat to the modified genetic resources that are responsible for maintaining the health and stability of production in the herd and that transmit desirable characteristics to the next generation (Barratt et al., 2019). Another noteworthy point is that the causative agent of Johne's disease is present in meat, milk, and manure of infected animals. That is not destroyed by pasteurization processes and consequently, it may cause Crohn's disease, which is a chronic and costly disease in humans. On the other hand, the lack of early and accurate diagnostic tests and the inherent resistance of MAP to antibiotics and disinfectants have made it difficult to control this infection and have turned Johne's disease into a global challenge.

The costs spent to control this infection have also been completely different in countries depending on the financial management of diseases and the infection load in those societies. For instance, the total annual economic losses per cow in infected USA dairy herds range from US$21 to US$79, while in Canada it is CDN$49, in Australia ranges from A$45 to, in the UK it is GBP27, in Nederland it is €67, and in France it is €234 (Chi et al., 2002; Groenendaal et al., 2002; Dufour et al., 2004; Stott et al., 2005; Tiwari et al., 2008; Groenendaal & Wolf, 2008; Pillars et al., 2009; Shephard et al., 2016; Verteramo Chiu et al., 2018).

Obviously, in addition to the expenses spent on infection control, the economic and financial damage caused by the reduction in milk and meat production should also be considered. In this regard, the mean annual loss due to reduced milk production because of paratuberculosis infection in the USA is US$200±160 million (Losinger, 2005). Furthermore, the markets targeted by the breeders are another important factor affecting losses due to paratuberculosis infection. It has been shown that the farmers who sold breeder cattle were considerably more affected than those who sold all their cattle directly for slaughter or feedlots (Webb Ware et al., 2012). It is obvious that in both beef and dairy cattle, infection is associated with reduced fertility, reduced cow weight, and reduced calf weight (Elzo et al., 2009). More interestingly, the same side effects can threaten animals even years after the infection. For instance, total annual losses per cow in 15 to 20 years after paratuberculosis infection is estimated to be GBP16 in the UK, €40 in France, €28 in Nederland, and US$17 in the USA (Groenendaal et al., 2003; Roussel, 2011; Bhattarai et al., 2013). The information regarding the damage related to other livestock has been very different and of course more limited. In New Zealand, sheep flocks infected merino flocks overpaid with a loss of about US$1.50 per ewe each year, almost three times higher than meat sheep breeds, while the mean annual mortality rate of sheep in this country due to infection ranged between 6.2 and 20.0% (Bush et al., 2006; Windsor, 2014; McGregor et al., 2015). In the UK, the annual economic losses due to sheep infection by paratuberculosis have been GBP 0.4 to 32 million (Assessment of surveillance and control of Johne's disease in farm animals in GB, 2002). Also, paratuberculosis infection decreased the profit efficiency from 84 to 64% in Italian dairy sheep and goat farms (Sardaro et al., 2017). It should be noted that the indirect result of financial and economic losses caused by livestock conflict with this infection will be a significant decrease in the export of milk and livestock, which will cause a double loss to the economy and commercial trade in these countries. In a recent meta-analysis study by Rieger et al., (2021) in infected dairy farms in Switzerland, with a paratuberculosis prevalence of 6% in cattle of this country, a total loss of 11 095 652 € per year was calculated for a population of 559 900 dairy cows. Accordingly, milk yield reduction based on a lactation period of 305 days results in an economic loss of 4 304 577 € annually (Rieger et al., 2021). In another study by Philip Rasmussen et al., it was estimated that approximately 1% of gross milk revenue, equivalent to US$33 per cow, is lost annually in MAP-infected dairy herds. In this regard, one should also consider human infections resulting from this infection, directly or indirectly, by consumption of contaminated milk and meat (Rasmussen et al., 2022).

In contrast to the economic losses caused by the spread of samples with positive infection tests, the paratuberculosis-negative replacement is accompanied by an increase in economic profit. As recently indicated by Philip Rasmussen et al., an average benefit of US$76 per MAP-negative replacement purchase was estimated in major dairy-producing regions, equivalent to a premium of 13%, with higher premiums in regions characterized by below-average replacement prices and on-average farm-gate prices. To achieve this purpose, an accurate and accessible diagnostic method is necessary to recognize healthy and infected animals. In contrast to the economic losses caused by the spread of samples with positive infection tests, the paratuberculosis-negative replacement was accompanied by an increase in economic profit (Rasmussen et al., 2021).

THE ECONOMIC CONSEQUENCES OF PARATUBERCULOSIS CONTROL

An important question regarding the economic importance of infection control, especially in the long term, is whether the implementation of infection control programs and strategies in herds at risk of infection can assure buyers that their purchased herd will be non-infected in the long term (Tiwari et al., 2008).

Risk stratification

As a first step in this regard, risk stratification of farms is strongly suggested. Based on the studies, firstly, it seems that buying from low-risk and even medium-risk pastures does not increase the risk of livestock becoming infected with infection in the long term, and it is considered a safe thing to do. Also, in farms without evidence of disease, the risk of contracting this infection in 10 years will be almost zero. It is recommended that the issuance of a livestock sale certificate should be done based on the seller's crop risk stratification. Based on the study by Carsten Kirkeby in 2017 (Kirkeby et al., 2017), if a farmer bought a single animal from a low-risk farm per year, the simulations suggested that 93.4% of cases did not result in an infected herd. This means that in this scenario, there is only a 6.6% risk of MAP infection on the farm over 10 years. Therefore, it is quite obvious that the long-term results of the economic loss caused by infection and the spread of infection in new farms will also be strongly influenced by the infection risk classification strategy. It is interesting to note that even the purchase of livestock from medium-risk farms has not been associated with an increased risk of infection among host livestock. As shown by Kirkeby et al, the prevalence did not change considerably even when the farmer bought animals from medium-risk suppliers. In their survey, the risk of vertical transmission in the model is 39%. It means that 39% of calves born from the infected dam were infected and the possibility of spreading infection in vertical transmission is very important. Another point is that buying livestock from smaller herds significantly reduces the risk of infection in host herds. As indicated by Lu et al (Lu et al., 2010), the probability of infection fadeout decreased with the primary herd size. According to the studies, the initial spread of infection and the size of the herd will be two important factors that determine the economics of disease control. It seems that the most cost-effective control method for paratuberculosis depends on the herd's size and existing management quality (Smith et al., 2017).

Type of diagnostic test

Another factor related to the economics of infection control is the type of diagnostic test used to detect infection in primary samples. Diagnostic test accuracy, sensitivity, and cost-effectiveness of multiple diagnostic tests for predicting the disease state will be the importance of economic factors. The studies show that although the ELISA technique is the most cost-effective tool, PCR or FC testing is preferred more for decreasing prevalence, and both are assumed to be more sensitive for low-shedding animals (Aly et al., 2012; Robins et al., 2015). Some others believe that both ELISA and PCR methods to gather interpreted serially would be most cost-effective (Aly et al., 2012). Noteworthy, the lack of a non-invasive, accurate, fast, and available diagnostic method for Johne's disease- in every four stages- affects the economic importance of infection control.

Vaccination appoaches

As another point, vaccination approaches are considered an important factor in determining the economic status of infection control. An estimated average benefit of US$8.03 per animal per year is associated with vaccination in US dairy herds (Groenendaal et al., 2015). Therefore, by identifying factors related to the cost-effectiveness of infection control protocols in the long term, as well as factors affecting the economy of disease control and using them in the design of preventive models, it can be possible to conservation of genetic resources and minimize the economic losses caused by an infection in the long term.

Table 1. The novel physical diagnostic methods for Paratuberculosis

Methods	Object of study	Accuracy	Year	Ref.
Fluorescence imaging technique combining confocal laser scanning microscopy	MAP	-_	2006	(M. Le Puil et al., 2006)
NIR spectroscopy	Feces & Blood serum	Sen. &Spec. 100%	2006	(Norby et al., 2006)
Ramen spectroscopy	Milk+ sandwich immunoassay	-	2008	(Yakes et al., 2008)
Flow cytometry	lymphocytes	-	2011	(Andrew et al., 2011)
Ultrasonography trance abdominal	Trans- abdominal intestinal wall thickness	Sen. 100% Spec. 92.7%	2018	(Tooloei et al., 2016)
Hyperspectral image analysis -NIR Spectroscopy	Structural Mussels & Liver in Sheep	Sen. &Spec. 100% in Liver	2016	(Smith, 2016)
Confocal Microscope	MAP in cell	-	2017	(Mathie, 2017)
gene expression	Salivary gland	-	2019	(Sanjay Mallikarjunappa et al., 2019)
UV-vis spectroscopy + Gold Nano particle+ lateral-flow assay (LFA)	MAP recombinant protein	Sen. 84.2% Spec. 83.3%	2020	(Agrawal et al., 2020)
Immunofluorescence (IF) **Immunohistochemistry (IHC)** **Immunomagnetic Separation (IMS)**	Serum + recombinant MAP cell envelope proteins	Sen. 75% Spec.96%	2021	(Karuppusamy et al., 2021)
NIR spectroscopy and Aquaphotomics	Blood plasma	Sen. 100% Spec. 100%	2024	(Behdad, Pakdel, et al., 2024a)
NIR spectroscopy and Aquaphotomics	Saliva	Sen. 98% Spec. 100%	2024	(Behad et al., 2024)

*The sensitivity quantifies the model's ability to correctly identify the true positives of Johne's disease (Sen). The specificity is the ability of the model to correctly identify health or uninfected samples or true negative (Spec).

The Impact of Johne's disease on Human Health

It's worth noting that the agent responsible for Johne's disease can be found in the meat, milk, and manure of infected animals. This agent is not destroyed during pasteurization and may cause Crohn's disease in humans, which is chronic and costly. However, due to the lack of early and accurate diagnostic tests and the fact that MAP (the bacteria that causes Johne's disease) is resistant to antibiotics and disinfectants, it has become challenging to control this infection. As a result, Johne's disease has become a global challenge (Food Standards Australia New Zealand, 2005; A. G. Jordan1, L. R. Citer, C. G. McAloon, D. A. Graham, E. S. G. Sergeant1 and S. J. More, 2020). The recent study about the effect of MAP and Inflammatory Bowel Disease (including Crohn's disease and Ulcerative Colitis) introduced a new diagnostic approach to IBD using blood plasma or saliva in humans by NIR spectroscopy and Aquaphotomics. This study found that patients had a history of contact with livestock, engagement in agricultural activities, use of non-piped water, consumption of non-pasteurized dairy products, family history of IBD, or living in rural areas (Behdad, Massudi, et al., 2024). These findings suggest that contact with contaminated livestock -probably with MAP- and their products, including milk, meat, and their by-products, as well as exposure to contaminated manure and water, may significantly impact the IBD rate.

The Novel Physical Diagnostic Methods for Johne's Disease

Nowadays, the use of modern physical methods for diagnosing diseases has become preferable and desirable due to their non-invasiveness, reduction of time, cost, and side effects, and greater accuracy and precision with chemical methods. Reduction of environmental pollution, due to the lack of chemical materials consumed and the absence of chemical wastes have added to the advantages of these methods. Measurement based on molecular and atomic particles is the reason for the high accuracy of these methods.

Most of these methods are based on the interaction of electromagnetic waves with biological materials. Recent research based on modern physical methods includes fluorescence imaging (Le Puil et al., 2006), Near-infrared spectroscopy(Norby et al., 2006), Flow cytometry (Allen et al., 2011) Ramen spectroscopy (Yakes et al., 2008), Trans abdominal ultrasonography (Tooloei, M., Moghaddam, G., & Fahimi, 2016), Hyperspectral image analysis and NIR Spectroscopy(Smith, 2016), Confocal Microscope (Mathie, 2017), Monitoring the change of gene expression pattern in salivary glands (Sanjay Mallikarjunappa, Mounir Adnane, Paul Cormican, 2019), UV-VIS spectroscopy and Gold Nanoparticle (Agrawal et al., 2020), Immunohistochemistry, Immunofluorescence, Immunomagnetic separation (Karuppusamy et al., 2021), NIR Spectroscopy and Aquaphotomics (Behdad et al., 2024a) (Behdad, Pakdel, et al., 2024b) where the results presented in table1. Since early and non-invasive diagnosis of Johne's disease remains a global challenge, there is hope that the results of these studies will soon transition to the practical phase.

CONCLUSIONS

In recent years, animal health has become a significant concern due to the growing demand for healthy products from healthy animals. To meet this demand, breeding programs now consider new traits such as resistance to Johne's disease that are related to animal health. These programs require the non-invasive, accurate, fast, affordable, and available diagnostic methods, the development of which is the answer to the global challenge of early detection of Johne's diseases.

CONFLICT OF INTEREST

None declared.

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