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Paratuberculosis in Iran *Review Article*

A Review of the Paratuberculosis in Iran

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Received : 30 November 2020
Accepted : 25 August 2021
Published : 14 October 2021

DOI
10.25259/RVSM_1_2020

Quick Response Code:

ABSTRACT

The available information for decision-making and adoption of appropriate policies to control paratuberculosis in most countries is based on published studies in developed countries. Therefore, the present study is aimed to review the situation of Johne's disease (JD) in Iran, in a method to provide accurate information to implement effective programs to control the disease. This research is a systematic review based on valid databases inside and outside the country. The search was performed by keywords of Iran JD, cattle, sheep, goats, camels, buffaloes, milk, semen fluid, and a combination of them. Then, all articles that had necessary indexes were chosen. Unfortunately, despite the extended population of ruminants in the country and the higher infection rate of paratuberculosis in Iran in comparison with developed countries, the accepted strategies for the administration of paratuberculosis are voluntary and considered by ranchers. Basic control approaches are management modification, testing, culling, and vaccination, and implementation of these programs can be operative in control of the disease occurrence in Iran. Numerous mistakes in the design of studies limit the quality of evidence concerning the prevalence of paratuberculosis in the region.

Keywords: Paratuberculosis, *Mycobacterium avium* subsp. paratuberculosis, Ruminants, Livestock, Iran

INTRODUCTION

Mycobacterium avium subsp. paratuberculosis (MAP) causes paratuberculosis or Johne's disease (JD) in wild species and domestic ruminants. JD is characterized by a chronic wasting disease of ruminants that are caused by the acid-fast bacterium, MAP,[1] which characteristically causes continuous weight loss.[2] Paratuberculosis is well recognized as a disease of domestic ruminants. However, it more affects a broad of additional domestic and wild (free living or captive) species.[1,2] The clinical form of illness due to the long period of the commune usually is happened after 2 years. The most important symptoms observed in the primary form of cattle infection include chronic continuous weight loss and intermittent or chronic diarrhea,[2-5] watery diarrhea, resistance to treatment, losing weight, and decrease of milk production in cattle. Clinical disease may be caused by parturition, lactation, or other kinds of stresses.[6] In sheep, the clinical signs of JD are limited to chronic weight loss.[4,7-9] It can happen within 2 years of the animal age, which most animals succumbing to the disease at 3–5 years of age.[4,7,10] Diarrhea is not assumed to be a symptom of JD in small ruminants, except in the terminal stages of the disease.[2,6,7,4,11] The disease has affected the livestock industry across the globe. In goats, the disease is in favor of sheep in numerous respects.[12] Throughout the clinical disease, the single regular finding is weight loss despite apparently normal food intake.[10-12] Unlike cattle, diarrhea is rarely seen in

goats.[10,11,13] *Antemortem* diagnosis of paratuberculosis is demanding since the nature of the disease and the limitations of diagnostic tests. For these limitations, the purpose of diagnosis must be adequately defined so that the most suitable diagnostic procedure can be applied.[2,4]

In Iran, this disease was reported for the 1st time in cows in Jersey Abadan Oil Company in 1960 and 1961 by Khalili and Talechian. Subsequently, the presence of JD was reported by Maghami and Hedayati in one Holstein cattle. The existence of the disease in goats and sheep was approved by Tabatabaie *et al*. (1970).[14] JD is endemic in Iran, and it has been reported in sheep, goats, camels, buffaloes, and wild ruminants so far.[14] Iran has more than 85 million livestock and annual production of 383.58 million tons of milk and 37.1 thousand tons of meat.[14] However, the rate of economic losses of JD is not clear in Iran, but based on research, the importance of the issue is realized. It was evaluated in farms positive for JD, milk production had decreased in a production period and increased the distance between calving.[15]

Milk yield losses associated with high-risk cows in comparison to low-risk cows in lactations 1, 2, and 3 for mean daily yield were 0.34, 1.05, and 1.61 kg. Furthermore, accumulated 305-day yields were 103, 316, and 485 kg, respectively. The total loss was 904 kg over the first three lactations. Protein and fat yield losses associated with high-risk cows were significant, but mainly a quality of decreasing milk yield.[15]

The infection prevalence at the herd and animal level is often a key issue when decision or policy-makers determine whether the infection should be considered important or not and which measures to apply.[2,4]

During these years, various reports of JD have been published in Iran's livestock herds. However, there is not a regular and accurate monitoring program about the condition of this disease in Iran. These considerations are done in only a few regions of the country, and various diagnostic tests have been used to perform them. Therefore, because of differences in time, place, study method, and the result of these researches, it is not possible to accurately assess the situation of JD in Iran. Although, the prevalence of an infection at the herd and animal is the most crucial issue for determining whether the infection should be considered important or not and what decisions and policies must be taken and implemented. The present study aimed to review paratuberculosis in the population of livestock in Iran.

MATERIAL AND METHODS

Data source

The first search for existing publications reporting reviews and primary studies was carried out through searching the available databases. To collect the required data, the available electronic resources and database were used. This database includes reputable sites in the country such as Scientific Information Database, Magiran, Irandoc, and international databases such as PubMed and Google Scholar. Articles and dissertations were searched using keywords including Iran, JD, cattle, sheep, goat, camel, buffalo, milk, and a combination of them.

Selection criteria

For the last selection of studies, an initial screen for basic eligibility and a detailed appraisal of quality was performed. After the study selection, the relevant data were extracted. All articles and dissertations related to the prevalence of JD, contamination situation of milk, and semen to *Mycobacterium paratuberculosis,* have been evaluated until November 2020. Studies that discussed JD but did not report the rate of the prevalence of the contamination, studies with inadequate information, duplicate search results, or tests that could not be accessed, were deleted from them. According to these steps, 147 resources related to JD were found. Twenty-two sources and 59 articles due to being repetitive and being irrelevant to the subject were deleted from the study. Nine of the remaining sources were deleted by reading the abstract of the article and not having enough data. Finally, 56 articles and dissertations with proper quality entered into the systematic review process for the study.

Data extraction

Final articles entered into the study process were conducted by a pre-prepared checklist to extract the data. This checklist includes sample size, type of study, the prevalence of the disease, or infection. For more detailed data, please refer to the Table 1 .

RESULTS

Prevalence of JD in the livestock population of Iran

According to reports received in Iran, the prevalence of JD in cows and goats is 2–59% and 37–96%, respectively.[16] In other regions such as Ahvaz, the infection with the disease in slaughterhouses was 3%, 1.4–2%, and 96%, respectively, using ELISA test and Ziehl–Neelsen staining tests, in cattle, goats, and sheep. Furthermore, in other parts of Iran, the results obtained by ELISA, polymerase chain reaction (PCR), culture, and Ziehl–Neelsen staining techniques in which sera, milk, and feces were used were 3.6–25% and 17.3–37% in cattle and goats, respectively. However, the prevalence of the disease in cattle, goats, and sheep in other countries was reported at 2.31–7.4%, 0.3–45.1%, and 24–21.1%, respectively.[17] The significant point deduced from these reports is there are different obtained results

due to the use of different tests and the variety of hosting and species and environment, as well as differences in the methods of sampling and measuring them. It can be concluded that one of the main reasons for the difference in frequency of the infection is the type of diagnostic test. The cattle in a herd infected by MAP can be divided into four groups: (1) Exposing clinical symptoms and excreting the bacteria; (2) exposing subclinical symptoms and excreting the bacteria; (3) being infected by MAP but excreting the bacteria in a way that could be traced; and (4) not being infected.[18] Based on one of the results of the experiments and studies, it is found that the ELISA test shows less sensitivity in young animals and newly infected animals. It is due to insufficient antibodies produced by the animal that will be disappeared as the disease progresses and produced antibodies increase. Studies show that the actual prevalence of this disease in the Iranian livestock population is significant (the actual prevalence of cattle, goats, and sheep). As a result, it is necessary to pay attention to this disease and the economic damage caused by it. For this purpose, measures such as vaccination and separation of infants from infected mothers, restricting animals, and examining the performance of meat and dairy processing and pasteurization can be used.[16] The following formula of $TP = (AP + Sp - 1)/(Se + Sp - 1)$ can be used to calculate the actual prevalence, where TP is the proportion of truly infected animals with MAP, AP is the proportion of positive animals in ELISA, Se is sensitivity, and Sp is specificity. Furthermore, $\alpha = 0.05$ is considered as a statistical basis.[19] In conclusion, there is no relationship between the infection rate and species, age, gender, and the region of the livestock,[20] and the rate of the prevalence in cattle is less than in goats and sheep.[21]

Contamination of produced milk by *M. paratuberculosis*

Symptoms of this disease in cattle include loss of milk production, loss of weight, chronic and intermittent diarrhea, and at last death also in sheep and goats the symptoms can be emaciation, anorexia, and severe disability. The cause of JD is related to Crohn's disease in humans, so it is highly noticeable from a health humans' standpoint. The disease in humans is transmitted from mother to child, and in animals through contaminated milk and colostrum, food contaminated with feces, and the fetus, as well.[16]

Status of semen contamination produced by *M. paratuberculosis*

Finally, of the used semen samples, 42.9% were positive. The results of the prevalence of three of 11 studies sheep's semen samples show a 27% prevalence that confirms the existence of this bacteria in semen.[22]

DISCUSSION

In the present study, the apparent prevalence of JD at the individual level of cattle and the camel was obtained, which is higher than other species, and one reason may be the use of more sensitive methods including bacterial culture, PCR, and ELISA in performed studies in cattle and camel against the use of histopathological studies in sheep, goat, and buffalo. It was also observed in the apparent prevalence of JD in cattle using various study methods, the apparent prevalence using the PCR method is higher, due to the greater sensitivity than other methods. The prevalence of the disease in the individual level of dairy cows in Australia and the US is 22% and 75.8%, respectively.[23,24] The prevalence of the disease in the sheep and goat population in Europe is estimated at 72.79%.[23] The situation of JD prevalence in Iran showed higher infection compare to developed countries that have regular monitoring schedule and control in herds' level. Herd reservoir milk has 59%[25] and individual cow milk has 30%.[25] Infection in Iran that compare to the results of *M. paratuberculosis* infection situation in analysis studies in the world (28% and 32% infection in herd reservoir milk and individual cow milk, respectively)[26] shows a higher infection. Because JD is often subclinical, stockbreeders usually ignore this disease and do not realize its economic losses. Exact information on the amount of economic damage caused by this disease in Iran is not available, JD results in decreased milk production[27] and increased cow replacement costs, which has resulted in economic losses in the US dairy industry estimated at US$ 200 to US$ 250 million annually, or US$ 22 to US$ 27 per cow,[28] and also infection of JD in Iran compared to developed countries, the only common programs to control the disease is optional and is up to livestock breeders and there is no comprehensive and efficient program by the country's veterinary organization that is due to the existence of a significant part of the livestock population in semi-industrial and traditional units, spending more money, time, and effort related to important diseases such as tuberculosis and brucellosis, care of newfound and emergent diseases such as mad cow and avian influenza, hygienic control of raw animal products by the country's veterinary organization, and lack of credit resources. On the other hand, due to the long-term latency period and as a result of the increasing number of mass repellent animals, various transmission ways, high costs of diagnostic tests, elimination of vector animals. There are some problems in implantation to implantation of disease control programs. The basic procedure for JD control included vaccination, diagnosis, and elimination of infected animals, herd health management.[29] A vaccination schedule can be implemented in countries that do not implement tuberculosis testing and killing programs. Since Tuberculosis testing and killing related to the cow are in Iran, and it is very important, this program can be used to control JD in other ruminants. However, due to the

Table 1: Details of studies entered into the analysis stage.

Subject of study	Test used	number of samples	Number of positive cases (%)	Reference
Cattle	Bacterial culture	400	48 (12)	[22]
	PCR	120	19 (15.83)	[23]
	Bacterial culture	103	12 (11.56)	[24]
	Bacterial culture	363	15 (4.13)	[25]
	PCR	141	11 (7.80)	[26]
	PCR	90	24 (26.6)	[27]
	PCR	103	10 (9.7)	[24]
	ELISA	724	274 (15.89)	[1]
	ELISA	35.52	0.59 (1.66)	[4]
	Histopathology	90	6 (6.66)	[27]
	Histopathology	135	6 (4.44)	[28]
	Histopathology	250	5(2)	[29]
	Histopathology	293	9 (3.07)	[30]
	Histopathology	218	4 (1.8)	[31]
Sheep	Histopathology	85	5 (5.88)	[32]
	PCR	120	12 (10)	[23]
	ELISA	110	16 (14.54)	[26]
	Histopathology	65	1 (1.53)	[15]
	Histopathology	379	7 (1.84)	[20]
Goat	Histopathology	15	2 (13.33)	[32]
	Histopathology	80	2 (2.5)	[33]
	Histopathology	379	7 (1.8)	[20]
Camel	ELISA	90	2 (2.22)	[15]
	PCR	85 8	8 (9.41)	[23]
	PCR	95	7 (7.3)	[26]
	PCR	26	0 (0)	[15]
	PCR	50	5 (10)	[15]
Buffalo	Histopathology	100	3 (3)	[15]
	Histopathology	48	3 (6.25)	[31]
	PCR	60	15 (25)	[23]
Herd milk	PCR	100	94 (94)	[15]
	PCR	1.52	0.57 (37.5)	[4]
	PCR	110	12 (10.9)	[15]
	PCR	100	3 (3)	[15]
	PCR	86	3 (3.48)	[15]
Individual cow milk (seemingly healthy)	Bacterial culture	100	9 (9)	[15]
	Bacterial culture	80	6 (7.5)	[13]
	PCR	100	12 (12)	[15]
	PCR	80	14 (17.5)	[13]
	PCR	86	51 (59.30)	[15]
Individual cow milk (suspected of disease)	Bacterial culture	100	40 (40)	[15]
	Bacterial culture	80	17 (21.25)	[13]
	PCR	56	10 (17.85)	[15]
	PCR	80	25 (31.25)	[13]
	PCR	100	44 (44)	[15]
	PCR	86	35 (40.69)	[15]
Semen fluid	PCR	83	8 (9.63)	[26]
	PCR	112	14 (12.5)	[15]
	Bacterial culture	11	3 (27)	[15]
	Bacterial culture	63	10.8 (17.3)	[15]

same traditional breeding system as well as the high cost of vaccination, this action is not recommended. As mentioned, due to the presence of subclinical cases in the herd, timely diagnosis and elimination of them using diagnostic methods such as ELISA and PCR, which have a lower cost and ease of implementation and faster response that bacterial culture

can control the disease in the herd. However, using these tests are not common due to the cost and using the semi-industrial and traditional breeding system in the herds of Iran. On the other hand, the presence of sick animals in the herd is a risk factor for JD. Thus, the rapid elimination of animals with clinical symptoms is recommended.[30] Hygienic actions with livestock training that is executable in traditional breeding can be a great help to control disease in the herd. Since this bacterium can be excreted by feces and milk of infected animals, the main way of transmitting the disease is to take water and food contaminated by the feces of an infected animal. The highest susceptibility to the disease is seen in calves under 1 month of age, and this sensitivity rate decreases with age.[31] Separating the baby from mother at birth and not using colostrum and infected or suspected animal's milk and pasteurizing it, breeding young animals separately from adults, control of contamination of water and food with feces early change of bedding, and lack of maintenance of different species of livestock next to each other are among the factors for promoting susceptibility to the disease. Eventually, due to the problems ahead, the disease is more common in cattle than in goat and sheep and its economic importance and existence of industrial livestock in country, various training programs can be started from industrial breeding units. Definitely, with incomplete information and knowledge about the JD situation in the country, it cannot be overcome. Disease control is possible when instrumental and information deficiencies are covered by providing better organization and long-term planning by the country's veterinary organization.

CONCLUSION

Paratuberculosis remains an immense problem in Iran and the infection leads to large financial losses in affected herds. The possible connection to Crohn's disease in humans further emphasizes the need for an increased effort to control this infection. One of the major obstacles is the lack of sensitive and specific diagnostic tests, especially in young and subclinically infected animals. There is also still far too little known about the factors affecting the development of clinical disease and a lack of knowledge of the basic immunopathogenic mechanisms. The focus should also be on methods for increasing the sensitivity of the PCR on feces. Meanwhile, it is important to apply the available diagnostic tools together with appropriate management practices in order to control the disease.

Acknowledgments

I would like to acknowledge all the people whom helped me through this article. I also like to mention Johne's disease in Iran: A systematic review and meta-analysis, which was a huge help in writing this study.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Khamesipour F, Afzal SS, Shojaat S, Nezaratizade S, Dehkordi BC, Kheyri P, *et al.* A review of the paratuberculosis in Iran. Res Vet Sci Med 2021;1:4.